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THE CORRECTION OF DISTORTED FLUID EQUILIBRIUM IN THE PRESENCE OF VASCULAR INJURY

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GENERAL OUTLINE OF THE PROBLEM

FREQUENTLY in sick children the severity of the secondary disturbance in physiologic function is more serious than the primary disease. Adequate supportive treatment therefore makes up a large and important part of pediatric practice. Some phases of this broad problem are better understood and more successfully managed than others. Much attention is directed toward bed rest in a favorable environment and to the proper nutrition of sick children. It is well recognized that the need for meeting the fluid requirements of a sick child is even more urgent than the need for food. Problems concerning the quantity and chemical composition of body fluids have received a great deal of attention. We know that normally about 70 per cent of the body weight is water. Of this total an amount equivalent to about 50 per cent of the weight is held in the tissue cells, while extracellular fluid amounting to about 20 per cent of the body weight is subdivided into 15 per cent in the interstitial spaces and 5 per cent in the blood stream as plasma. The amount of intracellular water is not readily subject to much variation, but distortions in the amount and distribution of extracellular water are common. Excessive fluid loss is always accompanied by a loss of salts, and it is now well recognized that the replacement of water and the appropriate amount and kind of electrolytes must go hand in hand. Thanks to the work of Gamble,[1] Hartmann,[2] Darrow,[3] Peters,[4] and many others the recognition and correction of dehydration and the distorted electrolyte equilibria of acidosis and alkalosis no longer present serious problems to the average clinician provided facilities are available for carrying out the necessary procedures. When appropriate amounts of fluid and electrolytes are administered by almost any available route, there is

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usually prompt correction of electrolyte imbalance, a return to the normal state of hydration with a restoration of a normal volume of circulating blood, and an adequate urinary output. Transfusions of blood may or may not be added to the above treatment, and the child usually makes a prompt and satisfactory recovery provided the primary disease can be overcome.

So many children respond well to these relatively simple supportive measures that we get to think of them as representing about all that need be considered in the way of restoring fluid equilibrium. Yet it is a common experience that some children, who may have the same primary disease and who may not appear to be in a worse condition when first seen than those who do well, do not show a satisfactory response to treatment such as we have just outlined. When fluid and electrolytes are replaced, their condition is transiently improved, but it is found difficult or impossible to maintain the improvement. The blood stream again becomes dehydrated in spite of the administration of fluid. At first thought this might be taken as an indication that the amount of water replaced is not adequate to keep pace with the loss from the body; yet this is not necessarily the case. There is often a gain in weight and the development of tissue edema at the same time that dehydration of the blood is noted. The unfavorable response results not because the deficiency in total extracellular fluid is not overcome but because too little of this fluid is being held in the blood stream and too much is accumulating in the interstitial spaces. As a result, the circulation is impaired because of the lack of a sufficient volume of blood, the urinary output is scanty, oxygenation is poor, and the electrolyte equilibrium remains distorted. In the face of all these handicaps the outcome is often fatal or at least the duration of the disease is greatly prolonged. There is too great a tendency to ascribe such an unfavorable response to some obscure toxic effect of the primary disease or to some unrecognized pathologic process. Actually in many instances the underlying physiologic disturbances are no more mysterious than those which are more readily amenable to treatment. The usual plan of therapy considers only the quantitative and qualitative replacement of fluid and electrolytes. In order to be adequate for many patients, the plan of treatment must also take into account the factors which regulate the normal partition of extracellular fluid.

Interstitial fluid and blood plasma are separated by the capillary endothelium. The two fluids contain essentially the same quantity and quality of electrolytes and dissolved crystalloids but differ widely in protein content. The interstitial fluid normally contains only a small fraction of 1 per cent of protein, while blood plasma contains about 7 per cent. The comparative compositions of the two subdivisions of fluid indicate that the capillary wall is normally freely permeable to water, dissolved electrolytes, and crystalloids but nearly impermeable to protein, which is largely retained in the vascular system. This selective

permeability of the capillaries is of tremendous importance in the distribution of fluid in the blood stream and the interstitial spaces. Protein colloid attracts and holds water. Since protein is retained by the capillary endothelium, the plasma protein is a primary factor in withholding water in the blood stream against the capillary blood pressure and other forces which tend to make water pass from the blood to the tissue spaces. For this reason, either a primary deficiency in plasma protein or a change in the permeability in capillaries to allow protein to escape into the tissue spaces would result in a decreased ability to hold water in the blood stream and a tendency for excessive fluid to accumulate in the tissue spaces. Since this is precisely the difficulty encountered in the patients who respond poorly to the usual supportive treatment, it is desirable to look for abnormalities in these essential factors as a possible explanation of the poor response.

Actually as seen clinically these patients present so many abnormalities at the same time and can be subjected to so few experimental studies that it is difficult to get far toward a better understanding of the various mechanisms involved. Much more can be accomplished under experimental conditions in animals where a simpler picture can be produced, where the welfare of the patient need not be considered, and where various experimental forms of therapy can be tried. In the next section of this paper the object is (1) to review and present new data obtained under experimental conditions which lead to an abnormal partition of extracellular fluid, (2) to emphasize observations which are useful for the recognition of the underlying abnormalities responsible for this condition, and (3) to compare the efficiency of various therapeutic measures in restoring and maintaining a more normal distribution of fluid.

EXPERIMENTAL STUDIES

Hypoproteinemia.—We have already postulated that a primary deficiency in plasma protein would produce a condition in which ability to hold water in the blood stream is reduced. Numerous studies, in which experimentally induced hypoproteinemia was the only abnormality, support this statement. Weech and his associates[5, 6] reduced the level of plasma protein in dogs either by withdrawal of large amounts of blood from which the plasma was separated and discarded and the cells reinjected after suspension in saline or by feeding a diet inadequate in protein. In such animals they demonstrated the occurrence of edema accompanied by a reduction in the volume of circulating blood. The administration of salt and water to such animals increased the edema. Chang[7] reported that persons with nutritional edema have a reduced plasma volume which returns to normal with the restoration of plasma protein. Such experiments leave no doubt that, even when all other factors are normal, a deficiency in plasma protein results in abnormal distribution of extracellular fluid.

Experimental Capillary Injury—Untreated.—Turning next to the possibility that increased capillary permeability which allows an escape of plasma protein might cause a similar reduction in blood volume, we again find ample experimental evidence for this view. Traumatic shock and burns are the most extensively studied conditions in which injury to capillaries allows a transfer of plasma elements into the interstitial spaces in the region of the injury. The traumatized area becomes grossly edematous while the volume of circulating blood becomes progressively diminished. Blalock and his associates[8, 9, 10] demonstrated that, following mechanical trauma or a burn to a large area of skin, the loss of plasma protein and fluid into the region of the injury is sufficient to account for the circulatory failure which results.

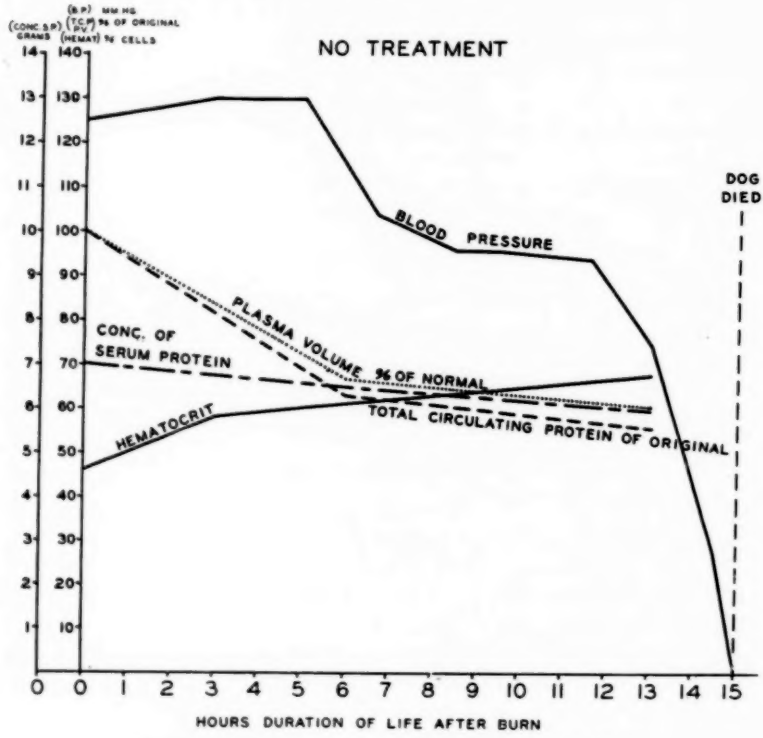

Fig. 1.—Changes observed in untreated burned animals.

For the present discussion the results obtained in dogs with burns of the skin of approximately one-third of the body surface serve to illustrate the sequence of events leading to circulatory failure. The dogs were anesthetized throughout the experiments. Measurements of blood and plasma volumes, hematocrit, serum protein, and blood pressure were made before and at intervals after the animals were burned. Six animals

were studied in this series. All died within 12 to 18 hours after the burn was inflicted. Since essentially the same changes were observed in all the animals, the results of only one typical experiment are presented graphically in Fig. 1. The values for plasma volume and total circulating protein are plotted as percentages of the original value determined before the dog was burned. The amount of total circulating protein was calculated by multiplying the plasma volume by the concentration of protein. One can see that a considerable loss of plasma volume has occurred by the end of the first six hours—in this case 32 per cent of the original volume. The swollen and edematous appearance of the burned area indicates that the fluid which has been lost from the blood stream is collecting in the injured region. Coincident with the loss of plasma volume there is a rise in the percentage of cells per unit volume of blood. The concentration of protein, however, does not increase with that of the cellular elements. On the contrary, there is a decrease in protein concentration, and, on calculating the total circulating protein, one finds there has been a loss of about 35 per cent of the original amount during the first six hours. This can mean only that plasma protein as well as fluid is being lost from the blood stream into the injured area. The blood is becoming more thick and viscous, and the circulatory apparatus must already be working under a handicap. In spite of the qualitative and quantitative changes in the blood, the blood pressure has not yet changed significantly. As time goes on the changes observed in the first six hours progress somewhat further. The percentage of cells increases gradually. The plasma loss continues until only 61 per cent of the original volume remains, while the total circulating protein is reduced to 54 per cent of the initial amount. It is not until about two hours before death that the blood pressure begins to fall significantly. Apparently at this point increased vasoconstriction and other compensatory mechanisms which have served to maintain pressure in spite of changes in the volume and character of the blood fail. Once the pressure starts to fall, fatal circulatory shock develops rapidly.

Circulatory changes similar to those produced in burns may develop in the absence of localized injury when general increased capillary permeability exists. We have already reported[11] that such a condition can be produced by the administration of toxic doses of guanidine hydrochloride to animals. The changes observed in such an experiment are given in Fig 2. The injury develops more slowly when induced by a toxic agent than when it is produced locally by heat. Except for the difference in time, however, the changes in plasma volume, protein concentration, total circulating protein, hematocrit, and blood pressure are similar to those which occur when the plasma loss is mainly into a localized injured area. Again we have a decrease in plasma volume and an increase in the percentage of cells. The serum protein concentration decreases or changes but little; this indicates a loss of plasma protein as

well as of fluid. Again it is not until there has been a loss of 30 to 40 per cent of the plasma volume and circulating protein that the blood pressure falls significantly. When compensatory vasoconstriction fails to maintain the blood pressure, fatal shock develops rapidly. When the fluid lost from the blood is distributed throughout the tissues generally rather than in a localized area, there is usually no evidence of gross edema. Ellis[12] has shown, however, that the water content of tissues increases as the blood stream becomes dehydrated in guanidine intoxication.

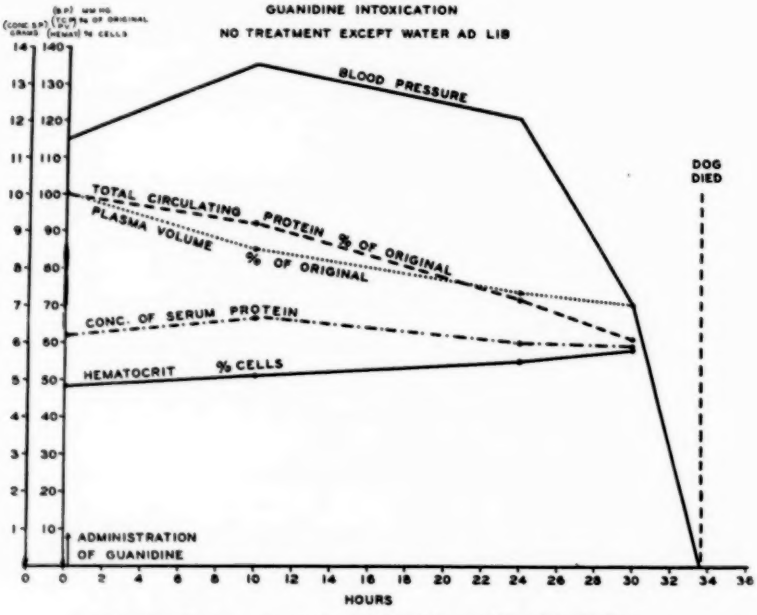

Fig. 2.—Changes observed in untreated guanidine intoxication.

These two groups of experiments demonstrate that the resulting abnormalities in partition of body water and in the circulatory system are similar when either a general or localized capillary injury has permitted an excessive transfer of plasma fluid and protein from the blood stream to the tissue spaces. In fact, no sharp division can be drawn between conditions involving local and general capillary injury. Freeman[13] has shown that prolonged vasoconstriction may lead to a general loss of plasma from the blood stream. The reason for the loss appears to be increased permeability of capillaries due to lack of oxygen[14] as volume flow is diminished in peripheral tissues. Hence the compensatory vasoconstriction which occurs as plasma is lost into a localized injured area often leads secondarily to a general increase in capillary per-

meability. Our observations show how rapidly a transfer of plasma from the blood stream to the tissues leads to disastrous circulatory changes.

It is puzzling at first that the transfer of a volume of plasma fluid, which has been shown[15] to be equivalent to about 2 to 4 per cent of the body weight, leads to as marked hemoconcentration and as serious circulatory impairment as does the loss of 15 to 20 per cent of the weight through dehydration. In simple fluid and electrolyte loss the concentrations of both plasma protein and cellular elements increase in the blood. With the rise in protein, fluid is drawn from the interstitial spaces to replace that which has been lost from the blood. Thus, it is not until the readily available extravascular reserves of water have been largely depleted that there is a serious reduction in the volume of circulating blood. On the other hand, when injured capillaries allow protein as well as fluid to escape, there is no increase in the concentration of protein in the remaining plasma and hence no means of drawing on the interstitial reserves of water. The blood stream becomes markedly dehydrated while the interstitial water is not depleted but, in fact, is increased. In conditions in which the capillary injury is not obvious, a useful early sign of the existence of increased capillary permeability is the observation that the cellular elements of the blood are becoming more concentrated without a parallel increase in the concentration of plasma protein. This can only mean a loss of plasma protein as well as fluid which, if it is progressive, will soon become disastrous. If one waits for the late sign of a fall in blood pressure as evidence of a loss of plasma volume, but little time is left for the institution of supportive measures.

Administration of Fluid to Animals With Capillary Injury.—Since we know of no direct means of decreasing the permeability of injured capillaries, we must direct our therapeutic measures toward restoring and maintaining an adequate volume of circulating blood in order to prolong the life of the subject until there is time for recovery from the injury. In view of the marked hemoconcentration and decreased blood volume which result from capillary injury, it seems that the intravenous injection of saline might improve the circulation. Some transient improvement in a falling blood pressure often results from such a measure. However, in animals with mechanical trauma Beard and Blalock[16] have shown that the intravenous injection of normal saline increases the loss of fluid and protein into the injured area. As a net result, the reduction in plasma volume is greater in treated than untreated subjects, and circulatory collapse is hastened rather than hindered.

We have already published results showing that the depleted volume of circulating blood in dogs with guanidine intoxication is not restored by continuous venoclysis.[17] A solution containing 0.9 per cent saline and 2 per cent glucose was administered over a period of several hours at the rate of 10 c.c. per kilo per hour to intoxicated dogs and to normal moder-

ately dehydrated dogs as controls. Measurements of plasma volume, hematocrit, plasma protein, and blood pressure were made at intervals during the treatment. The results obtained in one control and one poisoned animal of our series are reproduced in Table I.

TABLE I

EFFECT OF CONTINUOUS VENOCLYSIS IN A NORMAL DOG AND A DOG WITH GUANIDINE INTOXICATION

EXPERIMENTAL SUBJECT	TIME OF OBSERVATION	BLOOD PRESSURE M.M. Hg	Hb. %	HEMATOCRIT CELLS %	HEMATOCRIT PLASMA %	PLASMA VOLUME C.C.	BLOOD VOLUME C.C.	CONC. SERUM PROT. %	TOTAL AMOUNT SERUM PROT. GM.	AMOUNT FLUID RECEIVED C.C.	REMARKS
Control dog moderately dehydrated Wt. 13.1 kg.	Prelim.	95	114	52.9	47.1	522	1107	5.91	31.2	0	- - -
	7:20 P.M.	130	86	43.4	56.6	646	1142	4.56	29.5	1236	Fluid administration started 9:20 A.M.
	2:20 A.M.	130	95	41.8	58.2	-	-	4.75	-	2036	Fluid administration stopped 2:20 A.M. Duration 17 hr.
	8:20 A.M.	120	98	44.6	55.2	674	1222	4.96	33.4	-	No gross edema
	Urinary output 1250 c.c.										
Dog with guanidine intoxication Wt. 14.9 kg.	Prelim. to guanid.	117	89	40.2	59.8	694	1160	6.74	46.8	0	- - -
	Before fluid	113	92	45.1	54.9	594	1082	7.72	45.9	0	Fluid administration started 10:00 A.M.
	4:00 P.M.	124	76	37.0	63.0	-	-	6.06	-	775	- - -
	3:00 A.M.	134	92	41.6	58.2	544	934	5.89	32.0	2210	Fluid administration stopped at 3:00 A.M. Duration 17 hr.
	1:00 P.M.	80	94	44.6	55.4	488	882	5.26	25.7	-	Gross edema of subcutaneous tissues and extremities, small amount of free fluid
	Urinary output 600 c.c.										

The intravenous administration of fluid to the normal dehydrated dog results in a moderate and sustained increase in plasma volume with some decrease in the concentration of cells and plasma protein but with no loss in the total amount of circulating protein. There is a large output of urine and no evidence of gross edema. In the poisoned animal there is only a transient increase in the depleted plasma volume. As treatment continues, there is a progressive loss of both fluid and protein. The blood becomes more concentrated in cellular elements even while fluid

is being constantly introduced. The urinary output is scanty, and the dog becomes grossly edematous. Actually more of the administered fluid is retained by the dog with injured capillaries than by the normal dog. In spite of this, the blood becomes more concentrated because of the inability to hold this fluid in the blood stream. The plasma protein is already reduced before fluid is given. Further dilution of the remaining protein makes it easier for water and electrolytes to pass from the blood stream into the interstitial spaces. Simultaneously more protein escapes and accumulates in the extravascular fluid. Gross edema results, and the plasma volume is decreased rather than increased. The subcutaneous administration of fluid to intoxicated animals also proved ineffective. Such fluid is poorly absorbed, and large masses of edema remain at the site of injection for many hours. Taken as a whole, our experiments and those of other investigators show that the reduction in plasma volume secondary to either localized or general capillary injury cannot be corrected by the administration of aqueous solutions alone. Indeed, the condition tends to be aggravated by such a procedure.

Administration of Plasma and Fluid to Animals With Capillary Injury.—Since the failure of administered fluid to restore blood volume in the presence of capillary injury is apparently due to the loss of plasma protein, the next logical step in experimental therapy was to study the effect of replacement of plasma protein as well as fluid in dogs with vascular injury. We kept a group of animals for some time on the same diet, gave the same dose of guanidine per kilogram, and started treatment at about the same interval after the toxic dose was given. In this way we could obtain subjects with a fairly uniform degree of vascular injury. During the first hours of treatment sufficiently large transfusions of dog serum were given to replace the plasma volume and protein which had been lost during the preliminary period of intoxication. Fluid was then administered to some animals by continuous venoclysis and to others by subcutaneous injection. The results of therapy were followed at intervals by measurements of plasma volume, hematocrit, and plasma protein. Fairly uniform results were obtained in all the members of a given group. All the animals receiving preliminary plasma transfusions maintained a larger plasma volume during the subsequent hours of fluid administration than did the animals receiving fluid without plasma. This emphasizes again that lack of plasma colloid is largely responsible for the inability to hold fluid in the blood stream and that, only when the amount of plasma colloid is restored to normal, can one hope to maintain a normal plasma volume by the administration of saline solutions. Since all these animals had damaged capillaries, there was a gradual loss of the replaced plasma protein. The rate of this loss was greatly influenced by the route and rate of fluid administration. The best results in terms of retention of the replaced protein were obtained when only plasma was given by vein and fluid administration was restricted to the subcutaneous route. In contrast to the failure of

animals not given a preliminary transfusion to take up subcutaneous fluid, the dogs whose plasma protein had been restored absorbed fluid well. The good retention of protein was accompanied by the maintenance of a nearly normal plasma volume. Among the dogs receiving fluid by vein, a better retention of protein and a maintenance of a larger plasma volume resulted when more conservative amounts of fluid were administered at a slower rate. The results obtained in one dog given only fluid and in three given plasma followed by fluid are presented diagramatically in Fig. 3.

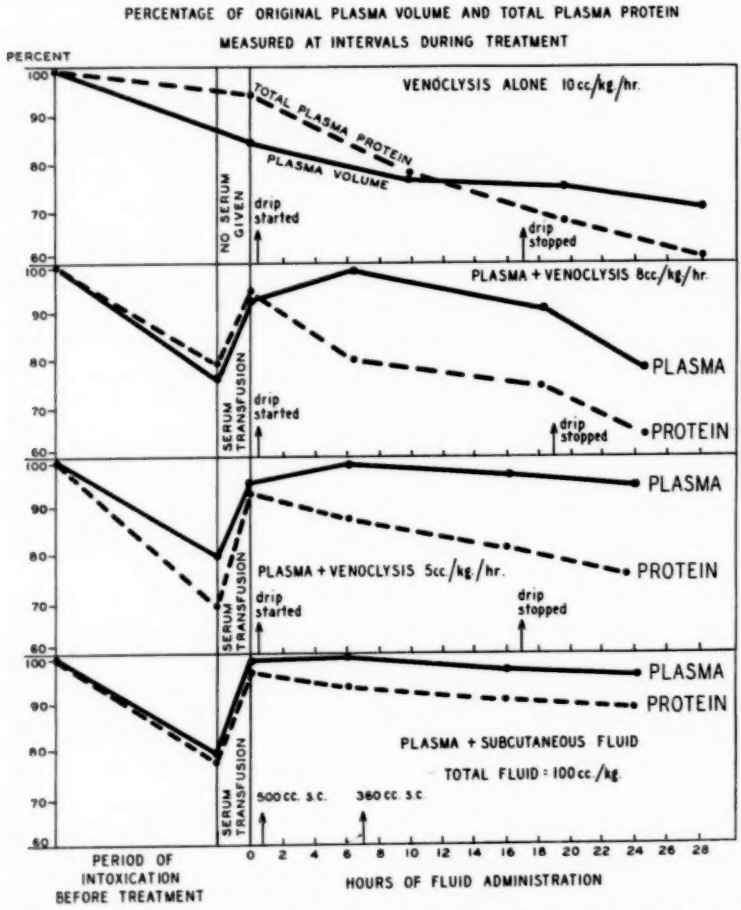

Fig. 3.—Effect of different forms of therapy on plasma volume and the total plasma protein in animals with general capillary injury.

From all the studies of experimental therapy in animals the conclusion is reached that in the presence of a primary hypoproteinemia or when plasma protein has been lost through capillary injury, a normal

partition of extracellular fluid can be maintained only after a restoration of plasma protein. In the presence of capillary injury precautions must also be taken to avoid measures which hasten the loss of the replaced protein.

CLINICAL APPLICATION OF EXPERIMENTAL RESULTS

The objection is often made with considerable justification that it is a far cry from observations made in experimental animals to an adaptation of such findings to clinical problems. There can be little question, however, of the general applicability of the fundamental principles influencing the distribution of fluid in the organism. Furthermore in this case, the unfavorable response to fluid administration demonstrated in experimental animals with hypoproteinemia and capillary injury is so similar to the clinical failure of such therapy in many patients as to leave little doubt that the same factors are involved in both instances. To be sure, clinical conditions are usually complex, and the simple factors of protein deficiency or capillary injury rarely play the primary role that they do in animal experiments. Nevertheless, so far as these factors are a part of the total clinical abnormality they will influence the response to therapy. It is well known that nutritional hypoproteinemia is fairly common among sick children.[18, 19] Injury to capillaries occurs in a variety of clinical conditions such as alimentary intoxication, septicemia, early congenital syphilis with edema and a tendency to hemorrhage, and severe infectious processes in general. Atchley[20] and Peters, Kydd, and Eisenmann[21] emphasize the occurrence of "medical shock" due to a decreased volume of circulating blood in diabetic coma and other conditions. Even prolonged severe dehydration often results secondarily in capillary injury as a result of inadequate circulation and oxygenation, which Landis[14] has shown promptly increases the permeability of capillaries.

On our service we have to treat many children with severe diarrhea. In the course of several years we have seen in this condition repeated illustrations of the principles just discussed. We have seen the favorable response and satisfactory prompt recovery following the restoration of fluids and electrolytes. We have also frequently seen fluid administration fail to restore an adequate plasma volume while gross edema developed, the urinary output remained scanty, and the circulation became progressively impaired.

We became most concerned with the frequency of this unfavorable response during our early use of continuous venoclysis. Once in operation this procedure, which was outlined by Karelitz,[22] offers a convenient route not only for giving fluid and electrolytes but for the introduction of blood or plasma, glucose, and special medication. Karelitz stressed that the amount of fluid administered should be considerably less than the amount that had previously been thought necessary and again emphasized the point previously made by Powers[23] that early transfusions

were important. In a small infant serious technical difficulties attend the continuous administration of fluid slowly enough not to exceed the optimum amount per hour. In our experience practically constant nursing care is necessary to maintain a regular, slow introduction of fluid. Often more fluid is administered at a more rapid rate than was ordered or intended. The high hemoglobin concentration in the blood of a dehydrated child makes it natural to delay transfusion until the need for water and electrolytes has been met. Thus in practice one tends to adopt the mechanical advantages of continuous venoclysis but to give fluid too fast with insufficient transfusions. The child with simple dehydration may respond satisfactorily to such treatment, but for him the simple administration of fluid subcutaneously would also be adequate. For the child with a nutritional lack of protein or with capillary injury, too rapid venoclysis leads to the same undesirable results observed in experimental animals suffering the same handicaps. The administered fluid is not retained in the blood stream but accumulates as edema in the interstitial spaces. The child is observed to gain weight progressively in spite of taking little or no food, and the blood stream remains dehydrated. If the capillaries are injured, protein is carried with fluid from the blood stream into the interstitial spaces. As an indication that these changes are occurring, one sees a progressive concentration of the cellular elements in the blood and a simultaneous dilution of the plasma protein. A continuation of such treatment can accomplish nothing toward the restoration of a more effective volume of blood. In these children as in the animals plasma protein must be restored before a normal disposal can be made of administered fluid and before a normal partition of extracellular fluid can be maintained. Adequate therapy must simultaneously replace fluid, electrolytes, and plasma protein. Furthermore in the presence of capillary injury the amount of fluid given must be conservative. Once the plasma proteins are restored, fluid is well absorbed when given subcutaneously. In our hands the best results have been obtained when only transfusions, glucose, and special medication, such as bicarbonate solution, were given by vein and the main volume of normal saline was administered by the subcutaneous route. We wish, however, to offer no general argument against the use of continuous venoclysis but only to emphasize again that fluid given by this route should be given slowly and in conservative amounts and that fluid should be accompanied or preceded by sufficiently liberal transfusions to restore and maintain the circulating plasma protein at a fairly normal level. No general rule nor even any preliminary calculation in a given patient can be made in regard to how much plasma protein may have to be administered. It depends not only on the degree of deficiency when treatment is started but also on how much of the replaced protein is lost as treatment progresses. Enough must be given to make possible

the retention of enough fluid in the blood stream to maintain an adequate circulating volume of blood. Again, a correlation of observations of fluctuations in weight and changes in hemoglobin and plasma protein concentrations serve as a useful guide in regard to the adequacy of plasma replacement. In a child taking inadequate food and not receiving transfusions of whole blood, a gain in weight accompanied by an increase in hemoglobin and a decrease in plasma protein means that plasma fluid and protein are being lost from the blood stream. This should be interpreted as an indication that further administration of plasma is necessary. In the presence of extensive capillary injury the amount of plasma required is often surprisingly large.

Replacement of plasma protein is most satisfactorily accomplished by plasma transfusions. The use of plasma avoids further burdening of the circulation with cellular elements which are frequently already in high concentration. Volume for volume plasma protein is introduced about twice as fast by giving plasma rather than whole blood. It is not necessary to match plasma with the recipient's blood. In general, reactions to the injection of plasma are less frequent than from the use of any of the more artificial preparations which have been suggested. The disadvantages of plasma are the extra technical difficulty and time required in preparing for a transfusion and the larger amount of blood which must be furnished by donors. In the circulatory collapse caused by an inadequate volume of blood a delay of a few hours may preclude the possibility of a favorable response; hence, if plasma cannot be procured without a delay, transfusions of whole blood should be given promptly and repeatedly. In this connection the value of having plasma on hand in some sort of a "plasma bank" can hardly be overemphasized when many patients with capillary injury must be treated.

Desiccated or lyophile serum as described by Mudd, Flosdorf, and coworkers[24] has given promise of being an ideal source of readily available material for supplying plasma protein. The dried serum can be kept indefinitely and redissolved in water as needed. Unfortunately reactions to the injection of redissolved serum have been frequent. Recent work suggests that the use of desiccated plasma rather than serum may avoid this difficulty.[25, 26]

SUMMARY

Restoration and maintenance of a normal amount of fluid and electrolytes in the body and a normal partition of the total body water comprise an important part of adequate supportive treatment. A normal partition of extracellular water in the blood stream and interstitial spaces is only possible when an adequate amount of plasma protein is present in the blood stream. In nutritional hypoproteinemia or following a loss of plasma protein through injured capillaries there is a dis-

tortion of fluid distribution in that too little is retained in the blood stream and too much accumulates in the tissue spaces. Thus edema of the tissues and dehydration of the blood may occur simultaneously.

When plasma protein is deficient, the administration of fluid alone fails as a means of restoring an adequate volume of blood. Indeed such measures often result in a greater loss of protein through injured capillaries. A useful early sign that fluid administration is leading to this undesirable result is the observation of a gain in weight accompanied by a progressive rise in the concentration of hemoglobin and a decrease in the concentration of plasma protein. Proper supportive treatment for such patients must include a replacement of plasma protein as well as of fluid and electrolytes. Better results in terms of retention of the replaced protein and hence of the replaced fluid in the blood stream are obtained when early liberal transfusions of plasma are combined with a conservative administration of fluid.

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THE VALUE OF B. PERTUSSIS VACCINE IN THE PREVENTION OF WHOOPING COUGH IN A CHILD-CARING INSTITUTION

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DURING the past two decades we have observed several epidemics of whooping cough in a model child-caring institution. These outbreaks have occurred at intervals of approximately five years, and, because of the high communicability of whooping cough, a large proportion of the children contracted the disease. As has been frequently pointed out, the most serious complication of this disease, bronchopneumonia, is much more likely to occur in children during the early years of life. In view of the fact that the institution cares for almost three hundred children ranging in age from 3 weeks to 4 years, the appearance of whooping cough causes considerable anxiety. It is, therefore, evident that any procedure which would modify or prevent this disease would be highly desirable.

In a previous outbreak of whooping cough we inoculated large groups of children with a *B. pertussis* vaccine, supplied to us by the New York City Department of Health, with the hope of checking the spread of the disease. The dosage of the vaccine varied from 20 to 60 billion organisms. The results, however, were disappointing, neither the incidence nor the severity of the disease having been affected. The interval between the time of inoculation of the vaccine and the development of the disease ranged from a few days to six weeks.

The failure to obtain satisfactory results with the use of this vaccine seemed to be explained later by Sauer,[1] who emphasized the necessity of employing larger dosages of the vaccine, namely, 80 billions of *B. pertussis* organisms, for the prevention of whooping cough. He also stated that immunity does not develop until three to four months following the inoculations. The vaccine used by Sauer was made from recently isolated hemolytic strains of the Bordet-Gengou bacillus which were grown on a medium containing 20 per cent human blood.

In 1935 when a *B. pertussis* vaccine, manufactured according to the specifications of Sauer, became available, we decided to test the value of this vaccine in the prevention of whooping cough in institutional children. As it was only a matter of time when an outbreak of whooping cough would occur, an excellent opportunity would thus be afforded for determining the efficacy of the vaccine under controlled conditions. Accordingly, children between the ages of 9 months and 4 years were

From the Home for Hebrew Infants.

paired with respect to age and sex, and one child in each pair was inoculated while the other served as a control. Thereafter alternate infants between the ages of 6 and 12 months were inoculated.* The vaccine was injected weekly, and in the course of two weeks a total dosage of 80 billion organisms was given.

Since September, 1937, we have been administering larger doses of vaccine than that originally recommended by Sauer. The dosage was increased for two reasons: first, because of the experimental work of Daughtry-Denmark,[2] who showed that 80 billion organisms brought about a four-plus complement fixation reaction in 63 per cent of the children inoculated, whereas 110 billion resulted in complete fixation in 97 per cent, and 140 billion, in 99 per cent of the children; and second, because of the failure of Siegel and Goldberger[3] in a well-controlled study to reduce the incidence of whooping cough among a group of institutional children receiving Sauer's vaccine in a dosage of 80 billion organisms.

We increased the dosage of the vaccine to 110 billion organisms from September, 1937, to May, 1938, and to 130 billion organisms from May, 1938, to October, 1939. Ninety-six infants received the 130 billion dosage. As the vaccine contained 10 billion organisms per cubic centimeter, a total of 13 c.c. was inoculated into these children. The dosage was divided as follows: first injection, 1.5 c.c. in each arm; second injection one week later, 2.5 c.c. in each arm; third injection one week later, 2.5 c.c. in each arm. The injections produced local reactions as well as a slight to a moderate elevation in temperature in most instances. Occasionally the inoculations brought about a temperature as high as 104° F., but in no instance was the reaction severe enough to cause any alarm. Several babies were inoculated with 160 billion organisms within a period of two weeks, but this dosage was discontinued because the reactions were too severe.

On Oct. 1, 1939, a noninoculated child developed whooping cough, and in the course of about two weeks several children in the same ward contracted the disease. Thereafter the disease spread rapidly to seven other wards in the institution. In these wards were children ranging in age from 15 months to 4 years. No new children were admitted to these wards during the epidemic which lasted five months. The total number of children intimately exposed was 137, 67 of whom had been inoculated with pertussis vaccine and 70 of whom had not been inoculated. The number of inoculated and control children in each ward was comparable as were the ages and sex for both groups of children. Of the inoculated children exposed, 7 had received a dosage of 80 billion organisms; 21, 110 billion; and 39, 130 billion organisms. The interval between vaccination and exposure was from 34 to 37 months

*When infants older than 12 months were admitted to the institution, they were paired according to age, and one child of each pair was inoculated.

in the 80 billion group, from 19 to 31 months in the 110 billion group, and from 0 to 22 months in the 130 billion group.

At the beginning of the epidemic the children who developed whooping cough were removed from the ward when the diagnosis was definitely established. As the epidemic progressed, this plan had to be abandoned because of the lack of available wards which could be used for isolation purposes. Since the children in the wards in which whooping cough appeared were mostly runabouts, it was impossible to prevent contact between those who developed the disease and those who had not as yet been affected. The exposure, therefore, was intensive and prolonged.

As we were interested in finding out not only whether pertussis vaccine reduced the incidence of whooping cough, but also whether it had any effect on the course, it was necessary to determine as accurately as possible the severity of each attack. Therefore the nurses were instructed to keep track of the number of spasms of coughing, of whoops, and of vomiting episodes in every child developing the disease, and a daily tabulation of these symptoms was recorded. At the end of each week the nurses in charge of the wards were required to give their clinical impressions of the severity of each case. Inasmuch as they did not know which children had been inoculated, their impressions were entirely objective. It may be added that when we finally estimated the severity of each attack, it was remarkable how closely the clinical impressions of the nurses coincided with those which we obtained by totaling the reported number of spasms, whoops, and vomiting episodes.

At this point it should be mentioned that there were 9 children who coughed so slightly that it was difficult to establish the diagnosis of pertussis. Neither coughing spasms characteristic of pertussis nor whooping was noted in these children. The duration of the cough varied from ten days to four weeks. The results of white blood counts were equivocal, and in two instances cough plates were obtained and were negative for *B. pertussis.** Six of these children had been inoculated, and three were controls. Although the diagnosis of whooping cough in these children was not definite, we regarded them as having very mild whooping cough because of the presence of an epidemic.

A comparison of the incidence and severity of whooping cough between control and inoculated children is recorded in Table I. It will be observed that of 70 control children, 58, or 82.8 per cent, developed whooping cough, whereas of 67 inoculated children, 24 or 35.8 per cent contracted the disease. Of the 24 inoculated children who had whooping cough, the disease was either very mild, or mild in 23, or 96 per cent, and moderate in one child, or 4 per cent. Thus, there were no severe cases in the inoculated group. On the other hand, of 58 control children who contracted whooping cough 28, or 48 per cent, had moder-

*In this connection it should be mentioned that a cough plate obtained in a child having characteristic whooping was positive for *B. pertussis*.

TABLE I

COMPARISON OF THE INCIDENCE AND COURSE OF WHOOPING COUGH BETWEEN CHILDREN INOCULATED AND THOSE NOT INOCULATED WITH PERTUSSIS VACCINE

GROUP	NO. OF CHILDREN EXPOSED TO WHOOPING COUGH	NO. WHO DEVELOPED WHOOPING COUGH	PERCENTAGE WHO DEVELOPED WHOOPING COUGH	COURSE			
				VERY MILD	MILD	MOD.	SEVERE
Control	70	58	82.8	11	19	16	12
Inoculated	67	24	35.8	16	7	1	0

TABLE II

COMPARISON OF THE INCIDENCE OF WHOOPING COUGH BETWEEN CONTROL AND INOCULATED CHILDREN ACCORDING TO INDIVIDUAL WARDS

WARDS	CONTROLS		INOCULATED	
	NO. OF CHILDREN	NO. DEVELOPING PERTUSSIS	TOTAL NO. OF CHILDREN	NO. DEVELOPING PERTUSSIS
2	10	10	9	4
12	10	9	5	2
6	9	9	10	7
7	9	7	10	3
8	11	7	8	0
9	8	7	11	3
11	9	8	11	4
A	4	1	3	1

ate or severe attacks while 27, or 52 per cent, had very mild or mild cases. There were no complications in either group although the epidemic was of moderate severity.

The incidence of whooping cough among the control and inoculated children in each of the eight wards in which the disease appeared may be noted in Table II. It will be observed that in seven of eight wards the incidence was lower in the inoculated groups of children. The ward in which there was no significant difference between both groups was ward A, where the mentally defective children were harbored. The incidence of the disease was unusually low in this ward due to the fact that most of these children were bedridden and therefore did not come in intimate contact with one another. The conditions in this ward were not comparable to those which existed in the other seven wards where the children were runabouts and where, as a result, the exposure was much more intensive.

It is apparent that *B. pertussis* vaccine brought about a significant reduction in the incidence of whooping cough as well as a modification of the course of the disease. As has been previously mentioned, the dosage of the vaccine varied from 80 to 130 billion organisms. In Table III the incidence of the disease in relation to the dosage of the vaccine is shown. It will be noted that the incidence was definitely lower among children receiving 130 billion as compared with those receiving 110 or 80 billion organisms. Thus, of 39 children receiving the 130 billion

dosage, only 8 or 20 per cent contracted whooping cough; of 21 children receiving 110 billion organisms, 12 or 57 per cent were attacked; and of 7 receiving 80 billion, 4 or 57 per cent contracted the disease. Two of the children in the 130 billion group were exposed to pertussis within one week following the last inoculation of the vaccine and both developed the disease. If these two children are excluded because of the probability that sufficient time did not elapse for the development of immunity, the incidence in the 130 billion group falls to 16 per cent. It may be added that one child was inoculated with 130 billion organisms five weeks prior to exposure and another child six weeks, and neither of these children developed whooping cough.*

TABLE III

INCIDENCE AND COURSE OF WHOOPING COUGH IN RELATION TO THE DOSAGE OF THE VACCINE

NO. OF ORGANISMS INOCULATED (BILLIONS)	NO. OF CHILDREN EXPOSED TO WHOOPING COUGH	NO. WHO DEVELOPED WHOOPING COUGH	PERCENTAGE WHO DEVELOPED WHOOPING COUGH	COURSE			
				VERY MILD†	MILD	MODERATE	SEVERE
0	70	58	82	11	19	16	12
80	7	4	57	3	1	0	0
110	21	12	57	7	4	1	0
130	39	8*	20	6	2	0	0

*Two of these children received the vaccine within three weeks of the onset of whooping cough.

†In nine children with very mild whooping cough, the course was so mild that the diagnosis could not be definitely established. Three of these children were in the control group; four, in the 110 billion; and two, in the 130 billion groups.

TABLE IV

INCIDENCE OF WHOOPING COUGH IN INDIVIDUAL WARDS IN RELATION TO THE DOSAGE OF THE VACCINE

WARD	CONTROL GROUP		80 BILLION GROUP		110 BILLION GROUP		130 BILLION GROUP	
	NO. OF CHILDREN	NO. DEVELOPING PERTUSSIS	NO. OF CHILDREN	NO. DEVELOPING PERTUSSIS	NO. OF CHILDREN	NO. DEVELOPING PERTUSSIS	NO. OF CHILDREN	NO. DEVELOPING PERTUSSIS
2	10	10	1	0	4	2	4	2*
12	10	9	-	-	-	-	5	2
6	9	9	1	1	5	4	4	2
7	9	7	2	2	4	1	4	0
8	11	7	-	-	-	-	8	0
9	8	7	1	0	5	2	5	1
11	9	8	-	-	3	3	8	1†
A	4	1	2	1	-	-	1	0

*One of these children developed pertussis two weeks after last vaccine injection.

†Developed pertussis three weeks after last vaccine injection.

In Table IV the incidence of whooping cough in relation to the dosage of vaccine is recorded for each of the eight wards in which the disease

*An infant who was one of a pair of apparently identical twins was protected with 130 billion organisms. The other twin, in the same ward, was not inoculated and developed whooping cough.

occurred. In six of these wards the effectiveness of the 130 billion dosage may be compared with that of the 80 or 110 billion dosage. It will be observed that in five of these wards the incidence of pertussis was lower among children receiving 130 billion organisms as compared with those receiving 80 or 110 billion.

The data therefore indicate that the children receiving 130 billion organisms had a higher degree of immunity than those receiving the smaller dosages. As previously stated, the children in the 130 billion group were inoculated 0 to 22 months prior to the epidemic, whereas the children in the 110 billion group were vaccinated 19 to 31 months, and those in the 80 billion group, 34 to 37 months prior to exposure to whooping cough. The question arises whether the superior results obtained with 130 billion organisms were due to the shorter interval between vaccination and exposure to whooping cough rather than to the increased dosage of the vaccine. There was, however, some overlapping in the intervals between vaccination and exposure in the 130 and 110 billion groups, eight children having received 130 billion organisms and nine, 110 billion nineteen to twenty-two months before the onset of the epidemic. A comparison of the incidence of whooping cough among these children is of interest; five of the nine children receiving 110 billion organisms contracted whooping cough, whereas none of the eight children receiving 130 billion developed the disease. Furthermore, when we divided the interval between inoculation and exposure to whooping cough into six-month periods, it was found that for the 110 and 130 billion group there was no increase in the incidence of the disease as the interval between inoculation and exposure became more prolonged; in other words there was no apparent loss of immunity in each of these groups with an increase in the time interval between vaccination and exposure. It should also be added that in the epidemic of whooping cough observed in an institution by Siegel and Goldberger the 80 billion dosage did not bring about a reduction in the incidence of whooping cough among young children despite the fact that the interval between inoculation and exposure was of the same range as that which prevailed for the children in our 130 billion group. It would seem, from the foregoing considerations, that the high degree of protection noted among children receiving 130 billion organisms as compared with those receiving 80 or 110 billion was due to the increased dosage of the vaccine rather than to the fact that these children had been inoculated more recently.*

Although the 80 billion or 110 billion dosage did not greatly reduce the incidence of whooping cough under the conditions of this investigation, the course of the disease was appreciably modified (Table V). It should be emphasized that the test of the effectiveness of the vaccine was quite rigorous, as the exposure in the wards was intensive and prolonged.

*The vaccine was obtained from the same manufacturer (Eli Lilly & Company) throughout the course of the study, and we are informed that there had been no change in the preparation of the vaccine during this period.

TABLE V

CLINICAL DATA OF INOCULATED CHILDREN WHO DEVELOPED WHOOPING COUGH

NAME	AGE AT TIME OF LAST INJECTION (MONTHS)	DOSAGE OF VACCINE	AGE AT ONSET OF WHOOPING COUGH (MONTHS)	INTERVAL BETWEEN VACCINATION AND ONSET OF DISEASE (MONTHS)	COURSE
G. R.	9	130	25	16	Very mild
K. G.	20	130	27	7	Very mild
S. F.	16	130	29	13	Very mild
R. L.	23	130	24	½	Mild
S. D.	13	130	22	9	Very mild
F. B.	16	130	16¾	¾	Very mild
J. G.	13	130	23	10	Mild
C. B.	8	130	22	14	Very mild
R. B.	7	110	30	23	Very mild
W. S.	8	110	29	21	Very mild
A. M.	8	110	30	22	Very mild
R. B.	6	110	30	24	Very mild
J. L.	7	110	27	20	Very mild
R. P.	8	110	34	26	Moderate
M. F.	9	110	34	25	Mild
J. L.	6	110	29	23	Mild
S. S.	10	110	32	22	Very mild
S. A.	6	110	30	24	Very mild
D. D.	9	110	36	27	Mild
J. S.	24	110	46	22	Mild
B. G.	11	80	47	36	Very mild
L. B.	11	80	48	37	Mild
G. S.	12	80	47	35	Very mild
G. R.	10	80	46	36	Very mild

TABLE VI

A COMPARISON OF THE INCIDENCE OF WHOOPING COUGH BETWEEN CONTROL AND INOCULATED CHILDREN DURING THE PRIMARY AND SUBSEQUENT OUTBREAKS OF THE DISEASE IN THE INDIVIDUAL WARDS

WARD	NO. OF CONTROL CHILDREN	NO. OF INOCULATED CHILDREN	PRIMARY OUTBREAK		SUBSEQUENT OUTBREAK	
			NO. OF CONTROL CASES OF PERTUSSIS	NO. OF INOCULATED CASES OF PERTUSSIS	NO. OF CONTROL CASES OF PERTUSSIS	NO. OF INOCULATED CASES OF PERTUSSIS
11	9	11	2	0	6	4
2	10	9	1	0	9	4
12	10	5	1	0	8	2
6	9	10	1	0	8	7
7	9	10	1	0	6	3
8	11	8	1	0	6	0
9	8	11	1	0	6	3
A	4	3	0	1	1	0
Total	70	67	8	1	50	23

The primary outbreaks of whooping cough in the various wards were the result of casual exposure in the hallways while the children were en route to the dining room or to the play room, whereas the subsequent outbreaks were due mainly to intimate and prolonged exposure within the wards. We thought it might be worth while to compare the relative proportion of control and inoculated children among the initial or

primary cases of whooping cough and among the subsequent cases. Table VI contains the results of this analysis. It will be noted that of nine children who were the first to develop whooping cough in eight wards, eight were controls and one was an inoculated child, whereas in the subsequent outbreaks fifty were control and twenty-three were inoculated children. Thus the proportion of control to inoculated children was 8:1 in the primary outbreaks and 2.2:1 in the subsequent outbreaks. We believe that this difference in the relative incidence of whooping cough for the two groups of children in the primary and subsequent outbreaks is of significance and would seem to indicate that the vaccine in the dosages used was more effective in preventing whooping cough when the exposure was casual than when it was intensive. It is probable that, if the dosage of the vaccine had been restricted to 130 billion organisms, the ratio of control to inoculated cases of whooping cough in the subsequent outbreaks would not have differed greatly from that in the primary outbreaks. In this connection it is of interest to add that Karelitz and Schick[4] have shown that larger doses of immune serum are required to protect children against measles under conditions of severe exposure.

TABLE VII

COMPARISON OF THE INCIDENCE OF WHOOPING COUGH BETWEEN INOCULATED AND CONTROL CHILDREN WHO WERE DISCHARGED FROM THE INSTITUTION FROM FOUR TO FORTY-EIGHT MONTHS PRIOR TO THE EPIDEMIC

DOSAGE OF VACCINE (BILLIONS)	NO. OF CHILDREN	AVERAGE AGE (YR.)	AVERAGE NO. OF MONTHS SINCE DISCHARGE	NO. DEVELOPING WHOOPING COUGH	PERCENTAGE DEVELOPING WHOOPING COUGH
0	151	5 1/3	30.7	22	14.6
80	120	5 5/6	32.6	2	1.7

Two hundred seventy-one children were discharged from the institution from four months to four years prior to the epidemic. One hundred twenty of these children had been inoculated with 80 billion organisms, whereas 151 had not been inoculated. The average age, as well as the average number of months since discharge, was almost the same for both groups. Questionnaires were sent to the guardians of these children in order to determine the incidence of whooping cough in these two comparable groups. As is shown in Table VII, the results of this inquiry revealed that only two in the inoculated group of children developed whooping cough, whereas twenty-two in the control group contracted the disease. The attack rate was, therefore, 1.7 per cent for the inoculated and 14.6 per cent for the control children. It should be emphasized that only one of the 271 children was exposed to whooping cough at home.

The high degree of protection afforded by the 80 billion dosage has been reported by a number of investigators who carried out studies in

child health stations or in the outpatient department of hospitals. The children who comprise such studies are, as a rule, not subjected to the type of exposure which existed in the institution. In those instances in which the exposure is intensive, as for example, familial, the 80 billion dosage does not appear as effective as when the exposure is extrafamilial. Thus, in a carefully conducted study by Kendrick and Eldering,[5] the attack rate among 1,850 children receiving 80 billion organisms was 2.3 per cent and among 2,397 control children, 15.1 per cent. However, of 83 household exposures among their inoculated children, 29 or 34.9 per cent developed whooping cough, and of 160 household exposures among the control children, 143 or 89.4 per cent contracted the disease. The relative proportion between control and inoculated cases of whooping cough was, in general, 6.6:1, but when the exposure was intensive, the ratio dropped to 2.6:1.

Household exposure, as previously stated, is of high degree and may be as severe as that which existed in the wards of our institution. Inasmuch as 130 billion organisms were required to reduce greatly the incidence of whooping cough at the institution, it is probable that this dosage will also prove more effective than the customary 80 billion dosage in protecting children intimately exposed to whooping cough in their homes. We therefore recommend the use of the 130 billion dosage for infants and young children having older sisters or brothers who have not had whooping cough and who may therefore bring the disease into the home. Whether this large dosage should be used for all infants and young children is a question. Inasmuch as intensive exposure may occasionally occur under circumstances other than household exposure, it would seem advisable to inoculate all infants and young children with 130 billion organisms.*

It is possible that larger amounts than 130 billion organisms can further reduce the incidence of whooping cough when the exposure is of severe degree. The double strength vaccine now available has made possible the use of larger doses than heretofore could have been employed with safety. We are now employing this vaccine at our institution and are inoculating 160 billion organisms. It may be added that the reactions have not been severe. Whether this dosage will be more effective than inoculation with 130 billion organisms will be determined by further observations.

SUMMARY

Sixty-seven young children who had been inoculated with *B. pertussis* vaccine (Sauer) and seventy children who had not been inoculated were intimately exposed to whooping cough in a child-caring institution. The ages and conditions of exposure were comparable for both groups. Of

*If one uses the double strength vaccine, the 130 billion dosage may be divided as follows: first injection, 1 c.c. in one arm; second injection, one week later, 2 c.c. in the other arm; third injection, one week later, 1.75 c.c. in each arm.

the 67 inoculated children, 24 or 35.8 per cent developed whooping cough, whereas of the 70 control children, 58 or 82.8 per cent were attacked. The severity of the disease was definitely milder in the inoculated group.

Three different dosages of the vaccine were employed, namely, 80, 110, and 130 billion organisms. Seven children received the 80 billion dosage; 21, the 110 billion; and 39, the 130 billion dosage. The incidence of whooping cough was considerably lower among those receiving 130 billion organisms, 20 per cent of the children having developed the disease as compared with 57 per cent in the 110 billion group and 57 per cent in the 80 billion group. It should be added that, although the incidence of whooping cough in the latter groups was not greatly reduced, the course of the disease was milder in these children as compared with the children not inoculated.

Two hundred seventy-one children were discharged from the institution from four months to four years prior to the epidemic; 120 had been inoculated with 80 billion organisms at the institution, and 151 had not been inoculated. The ages, as well as the average number of months which elapsed since discharge, were comparable for both groups. Two, or 1.7 per cent, of the inoculated children contracted whooping cough outside of the institution, whereas 22, or 14.6 per cent, of the control children developed the disease. The high degree of effectiveness of the 80 billion dosage among these children was probably due to the fact that the exposures were not intensive.

Under conditions of household exposure, the 80 billion dosage frequently does not prevent whooping cough although it may bring about a modification of the course of the disease. Inasmuch as household exposure may be comparable to that which existed in the wards of the institution, it is therefore probable that the 130 billion dosage would prove more effective than the usual 80 billion dosage in preventing whooping cough among children intimately exposed to this disease in their homes.

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THE COMPARATIVE NUTRITIVE EFFICIENCY OF INTRAVENOUS AMINO ACIDS AND DIETARY PROTEIN IN CHILDREN WITH THE NEPHROTIC SYNDROME

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IN PREVIOUS studies by Farr[7, 8] and Farr and MacFadyen[10] on the utilization of intravenous amino acids by young children with the nephrotic syndrome, the quantity of casein hydrolysate administered was small in relation to the total nitrogen intake. These observations demonstrated the feasibility and safety of parenteral nitrogen administration to this group of patients. The present study was undertaken to furnish information on the value of intravenous amino acids for the replacement of dietary protein in nephrotic children and to determine if the administration of large amounts of nitrogen parenterally would materially affect the chronic hypoaminoacidemia described by Farr and MacFadyen[11] or the characteristic plasma protein deficit.

CLINICAL COURSE OF PATIENTS AND EXPERIMENTAL PROCEDURES

Four children with the nephrotic syndrome, three males, S. G., aged 9 years, J. M., aged 8 years, and J. C., aged 7 years, and one female, R. Q., aged 8 years, were selected for study. All had been under careful observation on the wards of this hospital for at least one year, during which no significant permanent improvement in their nephrotic signs had occurred. Selected clinical and laboratory data on the course of the illness in each patient after admission to the hospital are shown in Figs. 1-4. Prior to beginning this study and throughout the experimental period the protein in the diet closely approximated the level for optimal nitrogen assimilation in these children as previously determined by Farr.[5, 7] The caloric intake of J. C. and R. Q. was 37 per cent in excess of basal requirements, and the intakes of J. M. and S. G. were respectively 29 and 33 per cent in excess. The basal requirements were estimated on the basis of the ideal surface area. This was calculated from the observed height and age, from which data the ideal weight was obtained from the Woodbury-Baldwin-Wood tables. From these data in turn the surface area was calculated by the formula $A = Wt.^{0.425} \times Ht.^{0.725} \times 71.84$. The caloric requirements were then calculated from the data given by Lewis, Kinsman, and Iliff.[14] In our patients the actual caloric excess over basal requirements was undoubtedly somewhat greater than the above figures would indicate because of the malnutrition present in all the children. At the time of beginning this study all the children

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were free from obvious acute or local infection, were afebrile, and, with the exception of S. G., had good appetites. Detailed summaries of the diets fed each child during the experimental periods are given in Table I.

TABLE I

SUMMARY SHOWING AVERAGE DAILY ORAL INTAKE OF PROTEIN, FAT, CARBOHYDRATE, AND CALORIES DURING EACH PERIOD OF BALANCE STUDY

PATIENT	PERIOD	ACTUAL WEIGHT AT END OF PERIOD (KG.)	IDEAL WEIGHT (KG.)	PROTEIN (GM.)	FAT (GM.)	CARBOHYDRATE (GM.)	CALORIES	PROTEIN (GM./KG.)	FAT (GM./KG.)	CARBOHYDRATE (GM./KG.)	CALORIES PER KG.
S. G.	1	24.5	26.3	72	60	111	1272	2.74	2.28	4.22	48
♂	2	24.6		49	66	90	1149	1.85	2.50	3.40	44
9 yr.	3	24.4		79	66	120	1391	3.00	2.50	4.55	53
	4	23.8		46	62	84	1078	1.75	2.36	3.19	41
	5	24.7		79	66	120	1391	3.00	2.50	4.55	53
	6	25.9		49	66	90	1149	1.85	2.50	3.40	44
	7	26.7		79	66	120	1391	3.00	2.50	4.55	53
	8	28.8		79	66	120	1391	3.00	2.50	4.55	53
	9	28.9		79	66	120	1391	3.00	2.50	4.55	53
	10	29.7		79	66	120	1391	3.00	2.50	4.55	53
J. M.	1	25.0	26.3	79	66	120	1430	3.00	2.50	4.55	53
♂	2	25.6		49	66	90	1184	1.85	2.50	3.40	44
8 yr.	3	23.7		79	66	120	1430	3.00	2.50	4.55	53
	4	23.7		49	66	90	1184	1.85	2.50	3.40	44
	5	23.2		79	66	120	1430	3.00	2.50	4.55	53
	6	23.4		49	66	90	1184	1.85	2.50	3.40	44
	7	23.3		79	66	120	1430	3.00	2.50	4.55	53
	8	23.5		79	66	120	1430	3.00	2.50	4.55	53
	9	23.2		79	66	120	1430	3.00	2.50	4.55	53
	10	22.7		79	66	120	1430	3.00	2.50	4.55	53
R. Q.	1	27.3	25.4	79	66	120	1391	3.10	2.60	4.70	55
♀	2	27.7		49	66	90	1149	1.90	2.60	3.50	45
8 yr.	3	26.5		79	66	120	1391	3.10	2.60	4.70	55
	4	26.4		49	66	90	1149	1.90	2.60	3.50	45
	5	27.7		79	66	120	1391	3.10	2.60	4.70	55
	6	27.3		49	66	90	1149	1.90	2.60	3.50	45
	7	26.3		79	66	120	1391	3.10	2.60	4.70	55
	8	26.7		79	66	120	1391	3.10	2.60	4.70	55
	9	25.7		79	66	120	1391	3.10	2.60	4.70	55
	10	25.2		79	66	120	1391	3.10	2.60	4.70	55
J. C.	1	19.3	18.6	53	53	120	1169	2.85	2.85	6.45	63
♂	2	19.8		23	53	90	931	1.24	2.85	4.84	50
7 yr.	3	18.8		53	53	120	1169	2.85	2.85	6.45	63
	4	19.6		23	53	90	931	1.24	2.85	4.84	50
	5	19.2		53	53	120	1169	2.85	2.85	6.45	63
	6	19.3		23	53	90	931	1.24	2.85	4.84	50
	7	19.2		53	53	120	1169	2.85	2.85	6.45	63
	8	19.8		53	53	120	1169	2.85	2.85	6.45	63
	9	19.7		53	53	120	1169	2.85	2.85	6.45	63
	10	20.0		53	53	120	1169	2.85	2.85	6.45	63

The planned calculated diet was fed to each child in every instance, except to S. G. during period 1. The nitrogen contents of the diets were calculated from standard tables[23] on food analysis.

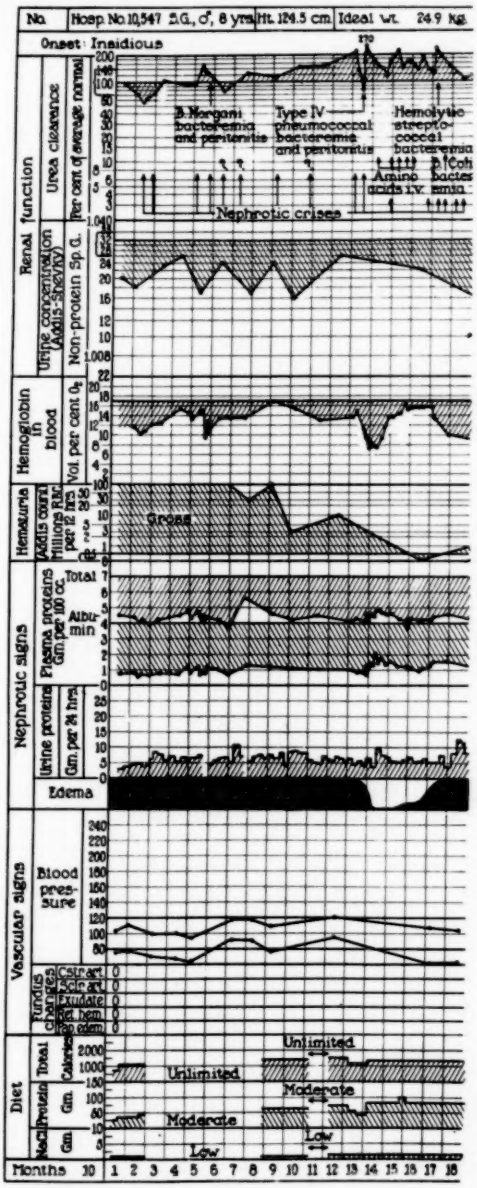

Fig. 1.—Graphic summary of selected clinical and laboratory observations on S. G. Illness began 10 months prior to admission to the Rockefeller Institute Hospital. The present study was carried out during months 14 to 16 of his hospital course. Note the frequent nephrotic crises in this child.

For a given day of any period the foodstuffs fed were identical except as acute clinical illness necessitated changes to a softer or liquid diet for short intervals. These modified diets were calculated to maintain the nitrogen intake constant. The reduced diets fed during injection periods

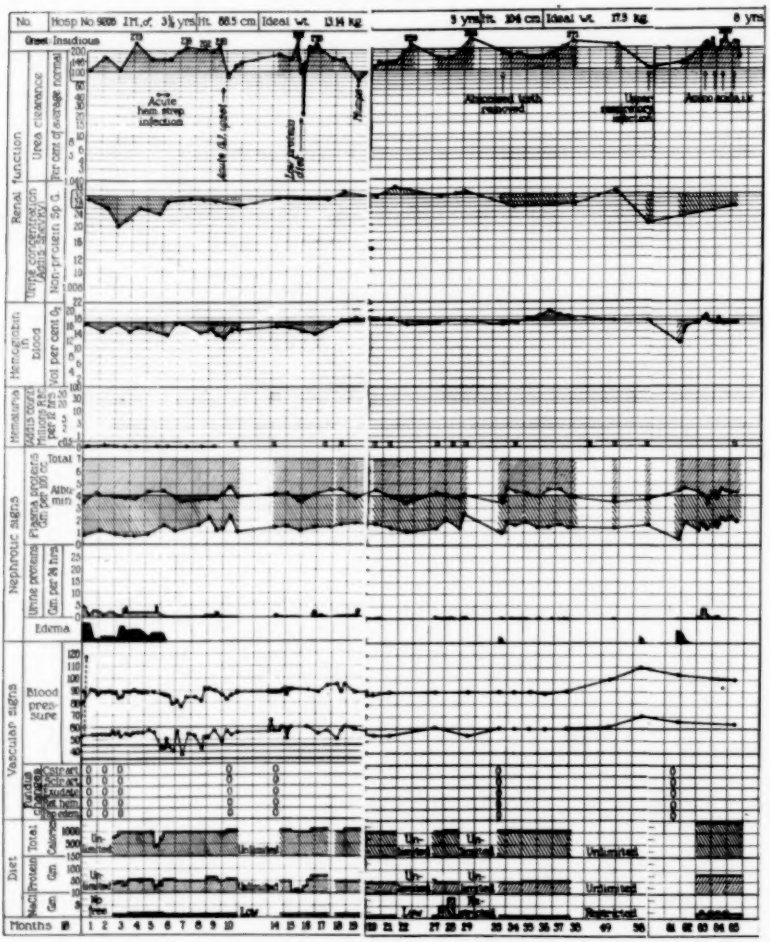

Fig. 2.—Graphic summary of selected clinical and laboratory observations on J. M. Illness began 18 months prior to admission to the Rockefeller Institute Hospital. The present study was carried out during months 63 to 65. Note the consistent elevation of urea clearance, the normal specific gravity of the urine, and low plasma proteins despite minimal or absent proteinuria.

were similarly standardized. On the few occasions in which there was vomiting, the vomitus was collected and analyzed for nitrogen. Blood specimens for renal function tests and blood chemistry studies were obtained once a week, the first day of each period. When the patients had acute episodes, additional blood chemistry studies were done daily.

Nitrogen balance studies were carried out for ten one-week periods. During the first, third, fifth, seventh, eighth, ninth, and tenth periods each child was fed his full diet. During the second, fourth, and sixth periods the protein and carbohydrate fractions of the diet were each

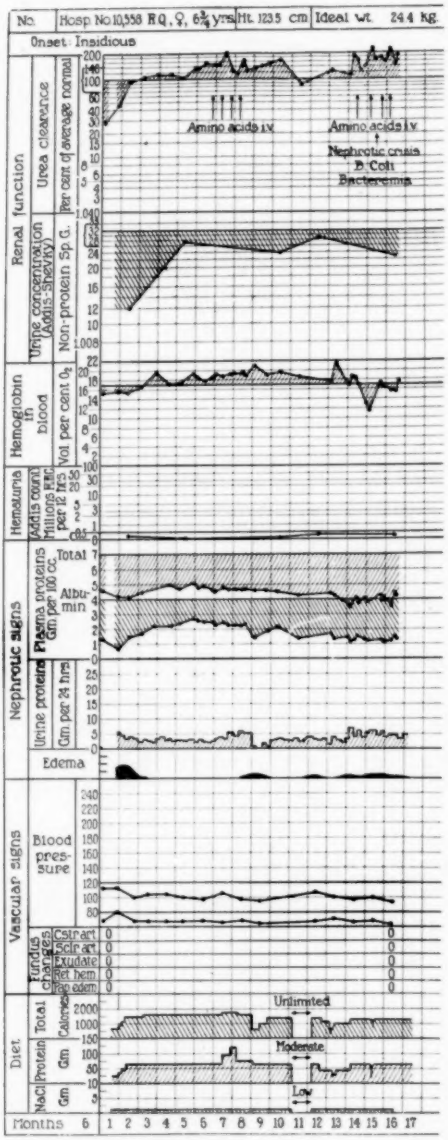

Fig. 3.—Graphic summary of selected clinical and laboratory observations on R. Q. Illness began 6 months prior to admission to the Rockefeller Institute Hospital. The present study was carried out during months 14 to 16. Note the rise in urea clearance after intravenous amino acid administration.

reduced 30 Gm. a day. Throughout the second and fourth periods 30 Gm. of casein hydrolysate and 30 Gm. of glucose were given daily intravenously. During the sixth and eighth periods 42 Gm. of casein hydroly-

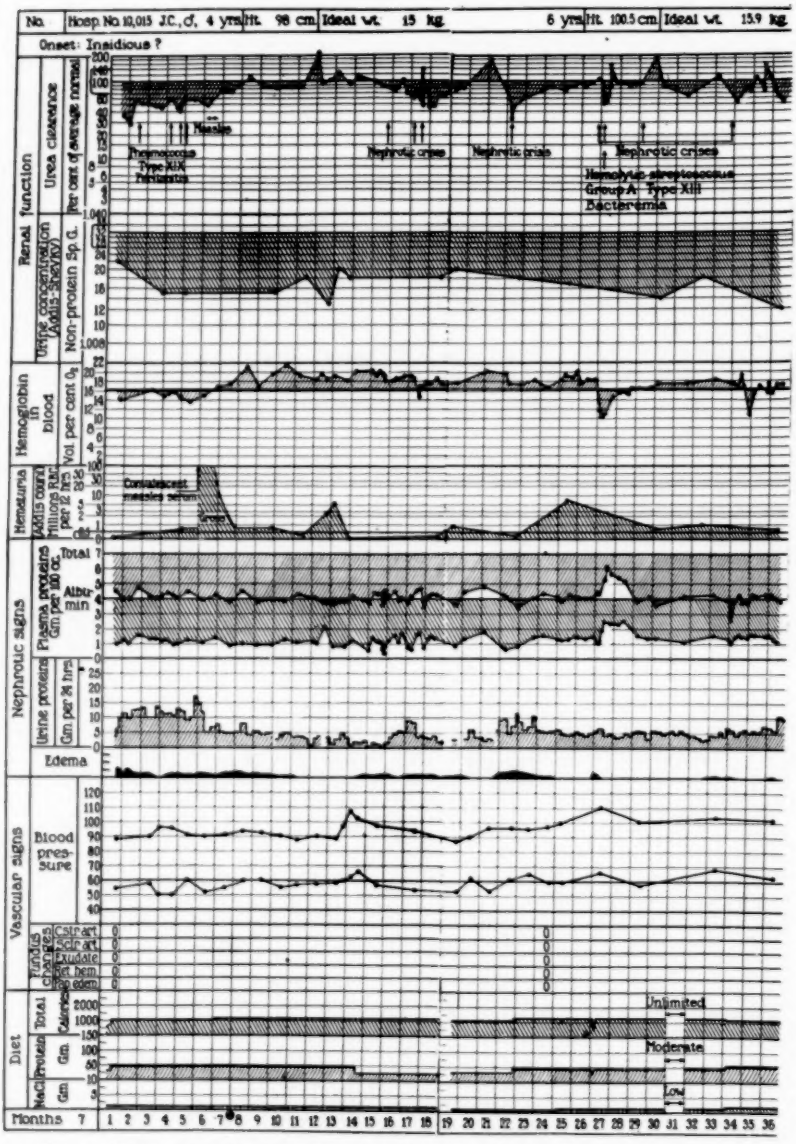

Fig. 4.—Graphic summary of selected clinical and laboratory observations on J. C. Illness began 7 months prior to admission to the Rockefeller Institute Hospital. The present study was carried out during months 34 to 36. Note the steady rise in urea clearance during the period of intravenous amino acid administration (months 34 and 35).

sate and 30 Gm. of glucose were given intravenously each day. Both the casein hydrolysate and the glucose were given as 10 per cent solutions. The total dose, given in three equal portions each day, was administered about one hour before each meal. For administration the desired volumes of casein hydrolysate solution and glucose solution were measured separately. A few cubic centimeters of the glucose were reserved for washing in all the amino acid solution at the conclusion of the infusion. The glucose solution and the amino acid solution were mixed, poured into an infusion flask and given by gravity as described by Farr.[8] When the infusion was almost completed, the remainder of the glucose was added and the last few cubic centimeters were usually pumped in by hand.

During the ten-week period covered by the present study, each of the patients had at least one febrile episode. Throughout the interval of this study S. G. remained in bed because of weakness. Three weeks previously he had been seriously ill with a pneumococcus Type IV bacteriemia followed by a *B. coli* bacteriemia. For over two weeks immediately preceding the present study he had been afebrile. Although his appetite was poor and remained so, he ate his full diet on all but a few days in the first period. He was afebrile except during the third, fourth, fifth, and sixth days of the first period when he ran a low grade intermittent fever reaching a maximum of 101.7° F. Throughout the second period he was afebrile. On the seventh day of the third period he complained of a slight sore throat and developed some hoarseness, malaise, and diarrhea. His temperature rose sharply to 105.4° F. at which time 15 Gm. of amino acids were given intravenously. His blood culture was negative. During the first day of the fourth period his temperature reached normal, and he remained afebrile until the fifth day of the tenth period when he developed coryzal symptoms and his temperature rose to 101.7° F. Subsequently his fever subsided rapidly, and by the seventh day of this period all coryzal symptoms had disappeared.

J. M. was permitted unrestricted activity about the ward throughout the study except during the fourth to seventh days of the fifth period when he was confined to bed with mild coryzal symptoms, abdominal cramps, diarrhea, and headache. On the fifth day of this period his temperature spiked to 103.5° F.; he complained of left lower quadrant pain and was given 20 Gm. of amino acids intravenously. His fever subsided within twenty-four hours, and he was free of complicating febrile episodes for the remainder of the study. Although this child had only the one day of fever noted above, he frequently ran a maximum daily temperature of 100.2° F. to 100.4° F. All temperatures were taken per rectum, and this degree of elevation was not considered to be clinically significant in this patient.

During the first three periods R. Q., who was permitted unrestricted activity, was afebrile. The evening of the sixth day of the fourth period she developed a slight cough, minimal nasal discharge, and fever of

101.2° F. The temperature returned to normal in two hours, and her other symptoms disappeared within twelve hours. On the sixth day of the fifth period she vomited breakfast, complained of headache, and was listless. The following day she complained of abdominal cramps. During these two days she was kept in bed and was afebrile. On the evening of the seventh day of the sixth period after a birthday celebration, she complained of abdominal pain and ran a temperature of 102.6° F. At this time her plasma amino acid nitrogen was found to be 1.87 mg. per 100 c.c. The following morning, which was the first day of the seventh period, her plasma amino acid nitrogen had fallen to 1.66 mg. per 100 c.c. Since this value was significantly below the critical level of 2.5 mg. per 100 c.c.,[11] 20 Gm. of amino acids were given intravenously on this day. During this same day the patient's temperature reached a maximum of 101.8° F., and a small erysipeloid spot appeared on the abdomen. The following morning at 8 A.M. her temperature was but 100.3° F. However, the plasma amino acids remained below the critical level, and an additional 18 Gm. of amino acids were given intravenously. Her temperature remained normal throughout the remainder of the second day of the seventh period, and she made an uneventful recovery. A blood culture taken at the beginning of this febrile episode was positive for *B. coli*. Subsequent blood cultures were sterile. This child remained free of fever for the remainder of the study despite the development of minimal coryzal symptoms on the sixth day of the tenth period. These subsided within twenty-four hours. At the end of the study period she was again normally active.

J. C. was afebrile throughout the first two periods, but on the sixth day of the third period complained of slight abdominal pain, which was accompanied by a mild diarrhea and fever of 101.6° F. The following day his temperature reached a maximum of 102.6° F., but there was no increase in severity of the abdominal pain or diarrhea. Blood cultures were sterile. He was free of complaints the following morning, which was the first day of the fourth period, and remained apparently well and afebrile until the fifth day of the tenth period when he developed coryzal symptoms. His temperature and appetite remained normal. On the sixth day of this period his temperature spiked sharply to 102° F., dropping quickly to normal and remaining there throughout the seventh and last day of the period. His coryzal symptoms also disappeared on the seventh day of the period, and he appeared normal. He was up and active throughout the study except during the febrile episodes noted above when he was kept in bed.

COLLECTION PROCEDURES: MATERIALS AND ANALYTICAL METHODS

The urine specimens were collected in clean sterile bottles, and whenever practicable the patient voided directly into the bottle. No preservative was used. At the end of every twelve hours each bottle was tightly

stoppered and stored in the ice box until the end of the seven-day period. At this time the entire urine specimen for the week was mixed thoroughly and aliquots were removed for analysis. Stool specimens were collected in clean pots, sent to the laboratory immediately after they were obtained, and transferred quantitatively to pyrex jars containing concentrated sulfuric acid. At the end of each period, the acid stool mixture was thoroughly stirred with a mechanical agitator and made up to a convenient volume; aliquots were removed for analysis. Two-tenths gram of carmine was given with the first breakfast in each period. The first stool containing carmine was taken as the first specimen of the period. No laxatives were necessary at any time. Vomitus was treated in the same manner as feces.

The enzymatic casein hydrolysate, prepared as described by Mueller, Kemmerer, Cox, and Barnes,[16] was generously furnished by Mead Johnson and Company. It was of the same lot (92-Z-38) as that used in other studies from this clinic.[7, 8, 9, 10] One hundred cubic centimeters of the solution, as prepared for intravenous use, contained 1.160 Gm. of nitrogen by Kjeldahl analysis. This was approximately a 10 per cent solution of the casein hydrolysate powder. On analysis of this casein hydrolysate solution, 50 per cent of the total nitrogen was found to be alpha-amino-carboxyl nitrogen by the ninhydrin-CO_2 method.[15] After hydrolysis with 6 normal HCl for twenty-four hours with complete hydrolysis of all peptides, the alpha-amino-carboxyl nitrogen rose to 75 per cent of the total nitrogen. Using Krebs' method, Hoagland[12] was unable to detect any δ-amino acids in the prepared solution of the hydrolysate. The material was prepared for intravenous use as a 10 per cent solution by the procedure previously described by Farr[8] with one modification. After the casein hydrolysate was put into solution at 100.0° C., it was placed in the ice box overnight before filtering through a Seitz filter and autoclaving. During this chilling period a large amount of flocculent precipitate was formed. Removal of this precipitate did not significantly change the red chestnut brown color of the solution. Unless this preliminary chilling was carried out, this material precipitated in the solutions stored in the ice box and had to be filtered through gauze immediately before use. Rabbit tests for pyrogens were omitted in the preparation of the material used in this study because in the many preparations previously made by us no pyrogen was found. However, in the present study each lot was subjected to preliminary clinical trial before being released for general use.

Standard macro-Kjeldahl procedures were used for determining total urine nitrogen, urine nonprotein nitrogen after deproteinization with trichloracetic acid, stool nitrogen, and vomitus nitrogen. Urine protein nitrogen was calculated by difference. Plasma amino acid nitrogen was determined by the ninhydrin-CO_2 method of MacFadyen and Van Slyke.[15] Plasma albumin was separated by Howe's method.[13] Total

plasma proteins and plasma albumin were determined by the Van Slyke gasometric micro-Kjeldahl technique.[19] Blood urea nitrogen was estimated by the hypobromite method of Van Slyke and Kugel,[20] and the same method was used for the determination of urea plus ammonia nitrogen in the urine for urea clearance tests. Hemoglobin was measured gasometrically by the method of Van Slyke and Neill.[21] The remaining clinical chemical analyses were performed by the methods routinely used in this laboratory.[1, 2]

RESULTS

The nitrogen balances are summarized in detail in Table II and Figs. 5 and 6. The nitrogen balances were generally positive with minimal variations typical of the nephrotic syndrome. Each patient exhibited a negative balance during at least one of the ten periods. During the first two injection periods, numbers 2 and 4, the total nitrogen intake was 1.32 Gm. per day less than in periods 1, 3, and 5, in which the diet was

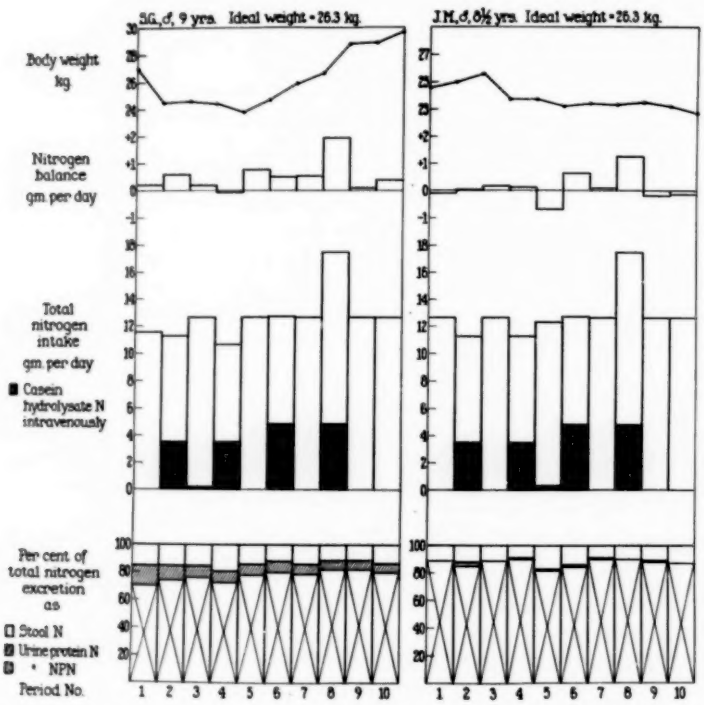
S.G., ♂, 9 yrs. Ideal weight = 26.3 kg.
J.M., ♂, 6½ yrs. Ideal weight = 26.3 kg.
Body weight kg.
Nitrogen balance gm. per day
Total nitrogen intake gm. per day
Casein hydrolysate N intravenously
Per cent. of total nitrogen excretion as
Stool N
Urine protein N
NPN
Period No.

Fig. 5.—Graphic summary of nitrogen balance data on S. G. and J. M. Note that during periods 2 and 4 when a smaller total nitrogen intake was partially furnished by intravenous casein hydrolysate, there was no decrease in nitrogen balance. Marked assimilation occurred in period 8 when the nitrogen intake was pushed above the usual level of maximum assimilation at 3.2 Gm. of protein per kilogram ideal body weight. Note the constant proportions of nitrogen excreted in urine and stool.

fed in full. Despite this slightly lower intake the nitrogen balance of three of the patients, J. M., S. G., and R. Q., was essentially the same as when the full diet was fed by mouth. During the third injection period (period 6) the total nitrogen intake was the same as in the succeeding and preceding periods. The nitrogen assimilation during this injection

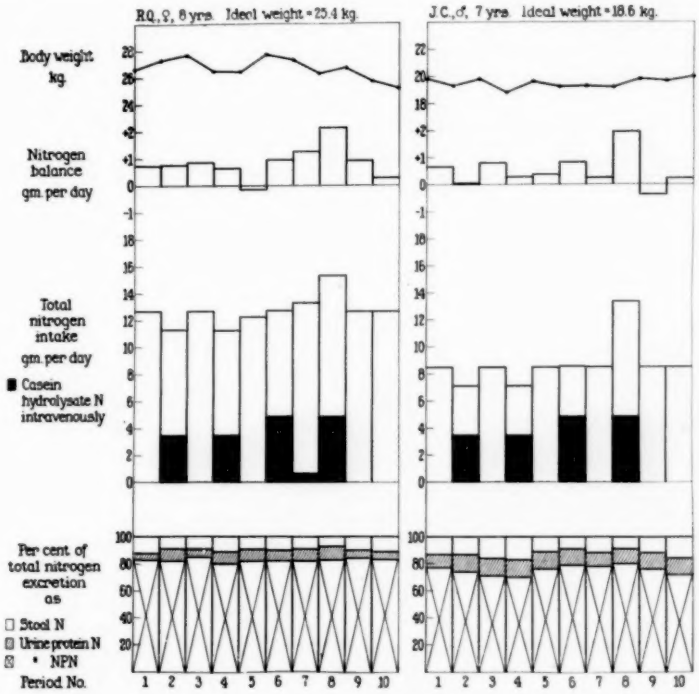
R.Q., ♀, 8 yrs. Ideal weight = 25.4 kg.
J.C., ♂, 7 yrs. Ideal weight = 18.6 kg.
Body weight kg.
Nitrogen balance gm. per day
Total nitrogen intake gm. per day
Casein hydrolysate N intravenously
Per cent. of total nitrogen excretion as
Stool N
Urine protein N
NPN
Period No.

Fig. 6.—Graphic summary of nitrogen balance data on R. Q. and J. C. Note that R. Q. was able to maintain a constant nitrogen balance through the first four periods though nitrogen intake was less during periods 2 and 4 when intravenous amino acids were given. J. C. was unable to maintain a constant nitrogen balance under these conditions. In period 6 when total intake by mouth plus injection was raised to level of previous oral intake, J. C. showed an increase in nitrogen balance. In both children marked assimilation occurred in period 8 when the nitrogen intake was greater than the optimal of 3 Gm. of protein per kilogram ideal body weight. Note the constant proportions of nitrogen excreted in urine and stool.

period tended on the whole to be somewhat greater than in the periods when no injections were given. In the case of J. C. the nitrogen assimilation was slightly less during the first two injection periods, when the intake was decreased, but during the third injection period the assimilation was definitely greater than during the periods of feeding alone. The uniformity of assimilation in all four patients during period 6, when 4.872 Gm. of nitrogen were furnished daily by intravenous casein hydrolysate, was surprising. Three of the patients showed a greater positive nitrogen balance during this period than during the

TABLE II

SUMMARY OF NITROGEN BALANCE DATA CALCULATED AS DAILY AVERAGE FOR EACH PERIOD OF SEVEN DAYS' DURATION (THE CASEIN HYDROLYSATE GIVEN INTRAVENOUSLY WAS A TEN PER CENT SOLUTION)

PATIENT	PERIOD	NITROGEN INTAKE BY MOUTH (A) (GM.)	NITROGEN LOSS IN VOMITUS (B) (GM.)	NITROGEN INTRAVENOUSLY AS CASEIN HYDROLYSATE (C) (GM.)	URINARY NON-PROTEIN NITROGEN (D) (GM.)	URINARY PROTEIN NITROGEN (E) (GM.)	STOOL NITROGEN (F) (GM.)	NITROGEN BALANCE OBSERVED (A–B+C)–(D+E+F) (GM.)
S. G.	1	11.584	–	–	8.044	1.559	1.761	0.220
♂	2	7.840	–	3.480	7.865	1.209	1.608	0.638
	3	12.640	–	0.248	9.626	1.160	1.883	0.219
	4	7.360	0.197	3.480	7.757	0.875	2.064	–0.053
	5	12.640	–	–	9.297	0.936	1.635	0.772
	6	7.840	–	4.872	9.770	1.064	1.353	0.525
	7	12.640	–	–	9.572	0.871	1.644	0.553
	8	12.640	–	4.872	12.744	1.086	1.729	1.953
	9	12.640	–	–	10.342	0.820	1.383	0.095
	10	12.640	–	–	9.740	0.924	1.577	0.399
J. M.	1	12.640	–	–	11.390	0.089	1.364	–0.203
♂	2	7.840	–	3.480	9.543	0.303	1.402	0.072
	3	12.640	–	–	10.887	0.050	1.336	0.367
	4	7.840	–	3.480	9.925	0.101	1.049	0.245
	5	12.640	0.691	0.331	10.656	0.180	2.131	–0.687
	6	7.840	–	4.872	10.214	0.132	1.739	0.627
	7	12.640	–	–	11.159	0.123	1.165	0.193
	8	12.640	–	4.872	14.350	0.078	1.547	1.537
	9	12.640	–	–	11.472	0.083	1.410	–0.325
	10	12.640	–	–	11.233	0.000	1.673	–0.266
R. Q.	1	12.640	–	–	9.835	0.679	1.396	0.730
♀	2	7.840	–	3.480	8.680	0.924	0.968	0.748
	3	12.640	–	–	10.082	0.669	1.030	0.859
	4	7.840	0.073	3.480	8.499	0.974	1.133	0.641
	5	12.640	0.378	–	10.218	0.997	1.179	–0.132
	6	7.840	0.008	4.872	9.632	0.952	1.142	0.978
	7	12.640	–	0.630	9.796	1.056	1.146	1.272
	8	12.640	2.151	4.872	11.034	1.331	0.848	2.148
	9	12.640	–	–	9.915	0.637	1.176	0.912
	10	12.640	–	–	10.208	0.827	1.315	0.290
J. C.	1	8.480	–	–	6.036	0.723	1.058	0.663
♂	2	3.680	–	3.480	5.247	0.904	0.951	0.058
	3	8.480	–	–	5.446	0.982	1.257	0.795
	4	3.680	–	3.480	4.824	0.900	1.162	0.274
	5	8.480	–	–	6.140	1.034	0.921	0.385
	6	3.680	–	4.872	6.082	0.916	0.737	0.817
	7	8.480	–	–	6.447	0.788	1.006	0.239
	8	8.480	–	4.872	9.138	1.269	0.991	1.954
	9	8.480	–	–	6.729	1.081	1.061	–0.391
	10	8.480	–	–	5.923	1.053	1.294	0.210

preceding period, while the fourth patient, S. G., showed a slight decrease to a value almost identical with the subsequent feeding period. During period 8 when the full diet was fed and in addition 42 Gm. of casein hydrolysate (4.872 Gm. of nitrogen) were administered intravenously, daily, all four patients had a marked increase in nitrogen assimilation as indicated by the increase in nitrogen retention. Little of

the nitrogen retained in this period was lost subsequently by any of the patients. None was lost by R. Q., and S. G., who were in positive nitrogen balance during the two following periods. J. C. was in negative nitrogen balance during the period immediately following the very high nitrogen intake. His loss during this period was less than the retention of the preceding period, and during the final period he regained a positive nitrogen balance. After the period of greatest nitrogen intake J. M. went into negative nitrogen balance for the remaining two periods. The magnitude of the nitrogen loss during these two periods was slight, and the total loss during the final two periods was considerably less than the quantity of nitrogen retained during the period of high intake. We have no data on how long this slight loss of nitrogen persisted after conclusion of the study since the patient was discharged.

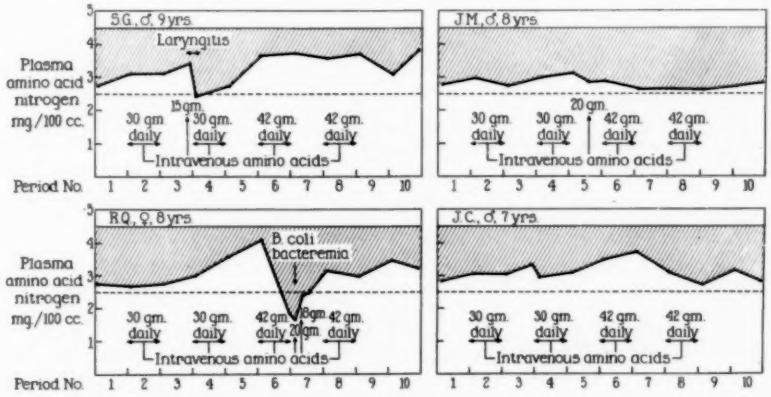

Fig. 7.—Graphic summary of changes occurring in plasma amino acid nitrogen concentration during the period of study. Note the average value for all four patients was well below the average normal of 4.50 mg. per 100 c.c. as shown by the shading. The critical level of 2.5 mg. per 100 c.c. of plasma is shown by the dotted line. In nephrotic crises the plasma amino acid nitrogen concentration drops below this value as shown by R. Q. at the end of period 6. Note that the intravenous injection of casein hydrolysate did not materially affect the final plasma amino acid concentration.

The administration of 210 to 294 Gm. of casein hydrolysate during a single week had no demonstrable permanent effect on the concentration of the plasma amino acid nitrogen in any of the four patients studied (Fig. 7). This has been our experience, up to the present time, in all nephrotic patients, totalling 25, to whom we have administered amino acids intravenously. In the present study, although there was no permanent increase in the plasma amino acid content toward normal, one patient, R. Q., showed marked temporary improvement. In this patient there was a gradual rise in plasma amino acid nitrogen from 2.68 mg. per 100 c.c. to 4.64 mg. per 100 c.c. from the second to the sixth period. During the sixth period the patient received a total of 294 Gm. of casein hydrolysate intravenously. However, the apparent improvement in

plasma amino acid concentration and the continued injection of casein hydrolysate intravenously did not serve to prevent the sudden development of a nephrotic crisis at the end of period 6. The patient's response to amino acid therapy during this crisis was identical with that observed in other patients who had not received amino acids intravenously immediately before a crisis developed.

In general, the patients tolerated the amino acid injections well. Individual variations in tolerance were, however, marked. All of the patients developed a flushing of the skin and spoke of a sensation of warmth during injection of the amino acid mixture. Abdominal cramps during injection were most marked in R. Q., while S. G. did not complain of abdominal cramps at any time. In those who developed cramps, the pain could be markedly heightened by increasing the speed of injection. Headache during some injections was complained of by J. C. All of the patients had retching at some time during injection periods. Usually it was not severe. In practically every instance retching followed after the patient began to complain of severe abdominal pain while the infusion was being run in. Severe vomiting during the injections developed in R. Q. during period 8. At this time the injections were being given in addition to the regular diet. Vomiting could usually be easily avoided in the patients by using a slow rate of injection. In general, vomiting was unusual when thirty to thirty-five minutes were taken for the infusion of 30 to 42 Gm. of casein hydrolysate. The development of retching during an infusion did not seem to affect the patient's appetite for the meal which was served within one hour after the injection was completed. During the third and fourth injection periods, numbers 6 and 8, R. Q. and J. C. developed submaxillary swelling during some injections. This swelling usually subsided within thirty minutes to an hour and apparently occasioned no pain or discomfort. No febrile reactions were encountered. Significant changes in pulse rate or blood pressure were absent. J. M., S. G., and J. C. seemed to acquire increased tolerance to intravenous casein hydrolysate during the period of study. During the last injection period when desired, it was possible to give the infusion to S. G. rapidly without eliciting disagreeable signs or symptoms. R. Q., on the other hand, never acquired any increased tolerance, and it was necessary to give her infusions just as slowly during the fourth injection period as during the first.

During the period of study J. C. showed an increase in urea clearance while injections were being given on alternate weeks. His urea clearance rose from 70 per cent of normal in the first period to an average of 120 per cent of normal in the eighth period. During periods 9 and 10 when no injections were given his clearance fell rapidly and was 60 per cent of normal when the study ended. There was no significant effect on the urea clearance of S. G. during the study. This patient had received numerous injections of casein hydrolysate during the weeks immediately

prior to beginning the study, and his clearance averaged about 160 per cent of normal throughout it. The urea clearance of J. M. consistently averaged about 200 per cent of normal throughout the study. This was not an unusually high value for this patient. In R. Q. there was a gradual irregular increase in the urea clearance from 115 per cent of normal to around 160 per cent of normal.

No characteristic trends were noted in hemoglobin values in these patients. The hemoglobin of S. G., which had fallen previously during the course of a severe pneumococcal infection, rose to near normal levels. There was no change in J. M. R. Q. showed a sharp drop in hemoglobin when she developed a crisis with *B. coli* bacteriemia, but at the conclusion of the study her hemoglobin was again normal. A sharp drop in hemoglobin in period 4 followed by a very rapid return to normal was observed in J. C.

Significant effects on the plasma albumin level were lacking. J. M. showed a slight rise in plasma albumin; S. G., a slight fall; R. Q. and J. C., no change. Effects on proteinuria were absent.

Addis counts on the urinary sediment[1] and Addis-Shevky concentration tests[2] done immediately after the conclusion of the nitrogen balance study indicated no unexpected deviations from earlier determinations.

DISCUSSION

The assimilation of nitrogen by these four children was more uniform than had been expected. The characteristic period of negative nitrogen balance preceding a nephrotic crisis[6, 8] was not seen in R. Q., who developed a crisis. The negative nitrogen balance seen in S. G. during period 4 followed a mild upper respiratory infection at the end of period 3 with a doubtful crisis the first day of period 4. The loss of nitrogen by S. G. during this interval was negligible, and none was lost during the period in which he developed a respiratory infection. J. M. showed the greatest evidence of "toxic" nitrogen metabolism as defined by Farr.[8] A daily nitrogen intake of 3 Gm. of protein per kilogram of ideal body weight was insufficient to maintain him in positive nitrogen balance in periods 1, 5, 9, and 10. The negative balance in period 5 appeared to result from moderate diarrhea during that period. No such explanation was apparent for the other periods in which nitrogen loss exceeded intake. It was noteworthy that when part of the nitrogen was furnished intravenously as casein hydrolysate, during periods 2 and 4, J. M. and R. Q. and, to a lesser extent, S. G. and J. C. were in positive nitrogen balance on a nitrogen intake below that in periods 1, 3, and 5. This apparent increased efficiency in nitrogen utilization and failure to go into a negative nitrogen balance in the period immediately preceding a nephrotic crisis appear to have been one effect of the intravenous administration of casein hydrolysate. All four patients maintained themselves

in positive balance during period 6 when the total intake by mouth plus intravenous nitrogen equalled the previous oral intake. All four patients showed a marked increase in nitrogen assimilation during period 8 when amino acids were given intravenously in addition to the full diet. Ability to utilize effectively large intakes of nitrogen in this instance was in contrast to earlier observations on the same type of patient by Farr.[5] In that study the nephrotic children were fed by mouth only, and no injections of amino acids were given at any time. He found that with oral feeding alone nephrotic children showed a maximum nitrogen assimilation when the daily diet contained 3.2 Gm. of protein per kilogram of ideal body weight, and lesser assimilation with greater nitrogen intakes. Subsequently Farr[8] showed that assimilation of dietary protein was altered by preceding intravenous injection of amino acids, which increased ability to utilize dietary nitrogen in excess of that furnished by 3 Gm. of protein per kilogram body weight. The same phenomenon was observed in the present experiment when the high nitrogen intake was furnished partly by the intravenous route. It is our impression that, in the present experiment, clinical evidences of toxicity from the very high nitrogen intake were lacking when the basic food protein intake of 3 Gm. per kilogram was increased to the nitrogen equivalent of 4.5 to 5 Gm. by amino acid injection; whereas in the earlier studies toxic signs were minimal when the high protein diet followed amino acid injections and marked when the same diet was not preceded by intravenous injection of casein hydrolysate. The absence of negative nitrogen balances preceding a crisis and the assimilation of increased quantities of nitrogen would both appear to have resulted from a decrease in the "toxic" nitrogen metabolism and to have been favored by the administration of intravenous amino acids. The mechanism whereby such a favorable effect was produced is not known.

Despite the evidence of a decrease in "toxic" nitrogen metabolism in these patients associated with the use of intravenous amino acids, there was no change in the plasma protein concentration in the three patients, S. G., R. Q., and J. C., showing the greatest retention of nitrogen. The plasma protein concentration did rise in J. M., who assimilated the least quantity of nitrogen during the period of study. This lack of correlation in nephrotic children between temporary changes in plasma protein concentration and nitrogen balance has been pointed out previously by Farr.[7, 8] The failure of the plasma protein concentration to increase in these patients when nitrogen was being assimilated may be due to a variety of factors and will be studied further.

In previous studies on the nitrogen balance of nephrotic children in crises,[6, 8] a negative nitrogen balance developed characteristically one to two weeks before the nephrotic crisis. This increased catabolism of tissue and plasma proteins and their precursors, indicated by an increased nitrogen excretion, suggested that nephrotic crises arose when nitrogen

depletion reached some as yet undefined critical phase. In the present study the development of a nephrotic crisis in R. Q. at the end of period 6 while she was in positive nitrogen balance would make this explanation untenable. In period 5 R. Q. had been in negative nitrogen balance; but during period 6 while receiving casein hydrolysate intravenously, she was in positive nitrogen balance and assimilating nitrogen to as great an extent as she had in any other period with a similar total nitrogen intake. Whereas in a previous study[8] the intravenous administration of 5 Gm. of casein hydrolysate daily for five days failed to prevent a crisis or to change the precrisis nitrogen balance from negative to positive, in the present instance the intravenous administration of 42 Gm. of casein hydrolysate daily for seven days reversed the nitrogen balance from negative to positive yet still failed to prevent the development of a crisis at the end of the seventh day. The drop in plasma amino acids at the moment of crisis in this instance must be explained on some basis other than catabolism alone. The explanation awaits further studies of amino acid physiology during these crises.

We did not observe the febrile reactions accompanying intravenous administration of casein hydrolysate reported by Shohl, Butler, Blackfan, and MacLachlan[17] and Shohl, Blackfan, and Higgins.[18] They used material furnished by the same manufacturers and of the same lot as did we. The difference in reactions observed was not due to differences in the product used. Differences in the method of preparation of the casein hydrolysate for intravenous use may account for part of the variability in reactions, but part may be due to differences in the subjects to whom it was given. They gave the material to infants; we gave it to children. Adults in our experience have behaved in the same manner as our children and were apparently generally similar to Elman's[3] patients in reactions. Shohl and his co-workers gave the material by continuous infusion. We gave the desired dose in three separate infusions spaced several hours apart so that complete metabolic equilibrium was attained after one injection before another was given. They attributed the fever, at least in most instances, to the great specific dynamic action of the casein hydrolysate.[18] The same specific dynamic action must have obtained in our patients. They observed no flushing of the skin which we observed uniformly. Although the increased heat loss obtained from skin flushing might explain the absence of fever in our patients, it would appear more likely that this was only one of several factors.

There can be no doubt, from a consideration of our data, that in our patients the intravenous casein hydrolysate completely replaced an equivalent amount of dietary nitrogen. These data do not answer the question whether a patient can be maintained indefinitely on intravenous casein hydrolysate as the sole source of nitrogen but strongly suggest that it is possible if *all other* food requirements were simultaneously met

in an adequate manner. Our evidence supports to this extent the data of Elman,[3] who has published reports indicating complete nitrogen equilibrium in adults given this amino acid mixture for the nitrogen supply over short intervals. In this connection a consideration of the distribution of nitrogen excreted in stool and urine and lost as proteinuria is interesting. During period 6 intravenous amino acids furnished 38 per cent of the total nitrogen intake in S. G., R. Q., and J. M. and 57 per cent of the total intake in J. C. Yet we found no significant change in the ratio of urinary nitrogen to stool nitrogen for this period compared with preceding and succeeding periods. Since the amount of roughage fed in the reduced diets during the injection periods was essentially the same as during noninjection periods, significant variations in stool nitrogen might not be expected. Failure to utilize amino acids injected intravenously would have produced a sharp increase in urinary nitrogen and this was not found. Previously Farr and MacFadyen[10] showed there was no immediate excretion of casein hydrolysate in the urine following intravenous injection, and Farr[7, 8] found no change in the ratio of urinary urea plus ammonia nitrogen to total nonprotein nitrogen during periods of injection of intravenous amino acids. All evidence thus far obtained by all investigators has been in agreement on the utilization of casein hydrolysate given intravenously for the satisfaction of nutritional requirements.

The effect of intravenous amino acids on the urea clearance was similar in all four patients but varied markedly in degree. A rise in urea clearance was noted in R. Q. and S. G. The urea clearance of J. M. rose to an average value slightly above that previously noted in this patient which usually was above 150 per cent normal. The effect on the urea clearance of J. C. was less obvious at the time. In the light of observations subsequent to this study it now appears that, while amino acid injections were being administered, J. C.'s urea clearance was at a maximum and that with discontinuance of the injections it fell again to lower levels. These effects on the urea clearance are in agreement with those previously reported by Farr.[8] From these and other unpublished data it appeared that one effect of intravenous amino acids in nephrotic patients was to increase the urea clearance when renal function was normal (urea clearance of 100 per cent of normal or above). As the urea clearance dropped below 100 per cent of normal, the effect of intravenous casein hydrolysate was sharply decreased so that no demonstrable change has been noted in patients with a urea clearance below 50 per cent of normal. The mechanism of this increase in urea clearance in "high" clearance nephrotic children was probably the same as that of the increased clearance following administration of high protein diets to these patients reported by Farr.[4] The similarity between these observations and the effect of dietary protein on the urea clearance of dogs, which Van Slyke,

Rhoads, Hiller, and Alving[22] showed to be due to changes in renal blood flow, suggests, but does not prove, the same mechanism for changes in clearance in our patients.

Neither in the present study nor in the previous work by Farr[7, 8] was there any evidence that the intravenous administration of casein hydrolysate materially shortened the course of the nephrotic disease in these patients, significantly affected in a favorable manner the severity of the nephrotic signs or symptoms of the disease, or influenced the ultimate outcome favorably. Failure to attain positive results in the treatment of the basic nephrotic syndrome to date has not excluded the possibility that greater experience in handling this amino acid preparation and greater knowledge of its physiologic properties may ultimately demonstrate it to be of value. At the present time we do not advocate its use in an attempt to treat the chronic plasma hypoaminoacidemia and hypoproteinemia of the nephrotic syndrome. Although no striking benefits have been observed in the disease itself with this type of treatment, we believe that intravenous amino acids are of definite value in the therapy of complications arising in patients with the disease, notably in nephrotic crises. As pointed out by Farr,[9] over a two-year period there was a significant decrease in the mortality in our nephrotic patients with pneumococcal bacteriemia. The mortality associated with pneumococcal bacteriemia in nephrotic crises dropped from 60 per cent to zero. No change in therapy had been made except for the addition of intravenous amino acids. We believe a definitely beneficial effect was obtained in patients with nephrotic crises with other types of bacteriemia as well. Although it is far too early to come to any conclusion regarding the efficacy of amino acids given intravenously under these conditions, *we believe the development of a positive blood stream infection in nephrotic patients to be a definite indication for intravenous amino acid therapy.* Treatment should be continued until the fasting plasma amino acid nitrogen concentration rises above 2.5 mg. per 100 c.c. This was the procedure followed in treating the patient R. Q., who developed a nephrotic crisis during the current study.

SUMMARY

1. Nitrogen balance studies of ten weeks' duration have been reported on four children with the nephrotic syndrome.

2. Replacement of 33 to 57 per cent of dietary protein nitrogen with nitrogen furnished by casein hydrolysate given intravenously increased slightly the efficiency of nitrogen utilization in these patients and within this range of substitution indicated that casein hydrolysate completely replaced dietary protein.

3. Intravenous administration to four nephrotic children of 30 to 42 Gm. of casein hydrolysate daily during alternate weeks for four injec-

tion periods was not followed by consistent increases in the concentration of plasma amino acids or plasma proteins. No adverse effects were noted.

4. Reactions encountered were limited to flushing of the skin, a sensation of warmth, abdominal cramps, nausea, and vomiting. The latter two reactions could generally be completely avoided by reducing the rate of administration.

5. Some of the physiologic effects following intravenous administration of casein hydrolysate were discussed.

6. We recommend the intravenous administration of casein hydrolysate as the primary therapeutic procedure in the treatment of nephrotic crises particularly when complicated by bacteriemia.

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VITAMIN K IN HEMORRHAGIC DISEASE OF THE NEWBORN INFANT

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Vitamin K has been shown to be necessary for the formation of prothrombin.[1-3] Lack of prothrombin in the circulatory blood causes a hemorrhagic tendency. This is a study of the relation of prothrombin and vitamin K to the bleeding tendency seen in the newborn period.

Prothrombin estimations were made by the method of Quick[1] which consists of mixing oxalated plasma with a thromboplastin solution, recalcifying, and measuring the time for clot formation. The thromboplastin solution used by us was made from fresh rabbit's brain. Using this method, we found the prothrombin time for twelve normal adults and twenty-five children to vary from 20 to 45 seconds, with 35 as an average.

Synthetic vitamin K capsules (2 methyl 1-4 naphthoquinone)* containing 1 mg. were given to mothers at the prenatal visit to the clinic when the attending physician estimated the pregnancy was within one week of term. The mother was instructed to take one capsule daily up to the time of delivery; the length of time varied from two to sixteen days. Prothrombin time estimations were made at the time of delivery on the blood of the mothers and on cord blood. There were sixty mothers' and fifty cord bloods obtained. At the same time similar tests were made on 100 control cases. Comparison of the prothrombin times for the control mothers and those receiving vitamin K shows that there is essentially no difference between the two groups.

The cord bloods show a prolonged prothrombin time in a large percentage of the control group, but none of the treated cases were beyond 120 seconds. It appears, therefore, that supplementary vitamin K in the mother's diet lessens the tendency to hemorrhage in the newborn period.

It is noticed from Table I that the prothrombin times of newborn infants tend to be longer than those of the mothers and also of normal persons. The prothrombin times of some of the control infants were as long as those seen in cases of hemorrhagic disease of the newborn, but there was no clinical evidence of bleeding at the time or subsequently. This indicates that there is some additional factor with low prothrombin of the blood causing hemorrhagic disease of the newborn

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*This material was kindly supplied by E. R. Squibb and Co.

TABLE I

PERCENTAGE OF CASES

	INTERVALS OF PROTHROMBIN TIME IN SECONDS				
	0-30	30-60	60-90	90-120	120+
Control mothers (100)	27	69	3	1	0
*Vitamin K mothers (60)	15	81.5	3.5	0	0
Control cord blood (100)	1	31	39	16	13
*Vitamin K cord blood (60)	0	64	34	2	0

*Mothers had received 1 mg. daily of 2 methyl 1-4 naphthoquinone prior to delivery for from two to sixteen days.

infant. In addition, no ill effects were observed in either the mothers receiving synthetic vitamin K or in their babies. In Chart 1 are plotted the cord prothrombin times compared to the number of days that the mother had received 1 mg. per day of synthetic vitamin K. There is no essential difference whether it was given for two days or for sixteen days.

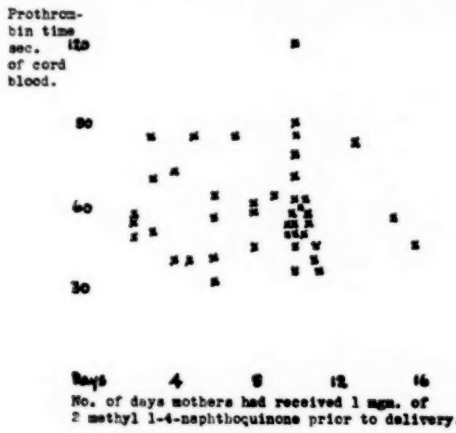

Chart 1.

In eleven cases of hemorrhagic disease of the newborn infant (Table II), the bleeding, clotting, and prothrombin times were estimated before and after arresting the hemorrhage by various methods of treatment. In these eleven cases the prothrombin times varied from 160 seconds to no clot formation at all. The bleeding and clotting times were elevated at the time of the prolonged prothrombin time. After treatment when bleeding had ceased, the prothrombin time was 95 seconds or less, and the bleeding and clotting times were within normal limits. Therefore, hemorrhagic disease is associated with prolonged prothrombin time, and with the arrest of the hemorrhage, the prothrombin time is decreased materially from the previous level.

TABLE II

BLEEDING, CLOTTING, AND PROTHROMBIN TIME BEFORE AND AFTER TREATMENT OF HEMORRHAGIC DISEASE OF THE NEWBORN INFANT

PATIENT	BEFORE TREATMENT			AFTER TREATMENT		
	BLEEDING TIME (MIN.)	CLOTTING TIME (MIN.)	PROTHROMBIN TIME (SEC.)	BLEEDING TIME (MIN.)	CLOTTING TIME (MIN.)	PROTHROMBIN TIME (SEC.)
1	9	3	160	3½	1½	55
2	12	6	280	3½	3	55
3	11	6½	190	4	2½	40
4	>15	15	∞		–	35
5	5	5½	235	3	2	50
6	9	14	∞	4	4	66
7	10	15	∞	4	2	95
8	–	–	230	–	–	65
9	8	12	230	3½	5	68
10	35	9	450	4½	7	60
11	3	4	380	–	–	60

TABLE III

RESULTS OF DIFFERENT TREATMENTS IN HEMORRHAGIC DISEASE OF THE NEWBORN INFANT

PATIENT	TREATMENT	PROTHROMBIN TIME (SEC.)		RESULT
		ADMISSION	AFTER TREATMENT	
1	Transfusion	380	165	Still bleeding
	Second transfusion		60	Bleed. stopped
2	Transfusion + 4 c.c. vitamin K*	∞	230	Still bleeding
			68	Bleed. stopped
3	Transfusion + 4 c.c. vitamin K*	450	60	Bleed. stopped
4	4 c.c. vitamin K*	230	65	Died of intracranial hemorrhage

*Natural vitamin K dissolved in corn oil, 700 units per cubic centimeter.

In Table III are the results of four cases of hemorrhagic disease of the newborn infant treated by transfusion and natural vitamin K* by mouth. Our experience for a previous five years in sixty-four cases of hemorrhagic disease shows that twelve, or almost 20 per cent, required more than one transfusion to effect a cure. The first patient, an example of treatment by transfusion of whole blood, received one transfusion and was still bleeding twelve hours later with only partial diminution of the prothrombin time. A second transfusion was required to effect a cure. The second patient received a transfusion and was given natural vitamin K by mouth, which was not retained; a similar result was seen as in the former case, and a second transfusion was necessary. The third patient was cured with one transfusion and 4 c.c. of vitamin K by mouth. The fourth patient had the prothrombin time lowered by natural vitamin K by mouth. Vitamin K by mouth is probably effective, as shown by the result in Case 4, but the possibility of its not being retained or of lack of absorption makes it an unsafe

*This material was kindly supplied by E. R. Squibb and Co.

procedure upon which to depend in an actual case of hemorrhage. There were no untoward results observed as a result of administering this to the infants.

Six cases of hemorrhagic disease (Table IV) were treated with synthetic vitamin K (2 methyl 1-4 naphthoquinone) intravenously, and the data as a result of this procedure alone are shown. The synthetic vitamin K was a powder, 10 mg. of which was enclosed in a glass capsule. The contents of this were dissolved in 100 c.c. of normal saline which was then boiled ten minutes for purposes of sterilization. This material should be kept out of the direct light and stored, if possible, in the refrigerator after it has been made up. Handled in this way, it is supposed to be effective up to one month. However, our experience in Case 5 (Table IV) indicated that it is probably not as potent after two weeks, because in this case 1.0 mg. in a solution made up for three weeks was given with a very slight effect on the prothrombin time in twelve hours and no effect on the bleeding. One-half milligram in a fresh solution was administered with a rapid effect, lowering of the prothrombin, and cessation of the bleeding in two hours.

TABLE IV

RESULTS OF TREATMENT OF HEMORRHAGIC DISEASE OF THE NEWBORN INFANT WITH VITAMIN K INTRAVENOUSLY

PATIENT	AMOUNT VITAMIN K (MG.)	PROTHROMBIN TIME		RESULT
		ADMISSION	AFTER TREATMENT	
1	0.5		120	Transfusion 1 hr. after vitamin K
2	1.0	160	40	Bleeding stopped
3	1.0	280	55	Bleeding stopped
4	1.0	190	40	Bleeding stopped
5*	1.5	235	50	Bleeding stopped
6	2.0		35	Died of massive intracranial hemorrhage

*1.0 mg. of an old solution of vitamin K was used with little effect; 0.5 mg. of new gave effect in two hours.

In six cases the prothrombin times were decreased by the vitamin K, and in four the bleeding stopped. In the last case we felt it was, because external bleeding had ceased. Case 1 was the first to be treated, and at that time we did not have the courage to wait longer than one hour without administering blood. None of the babies showed any ill effects as a result of the intravenous administration of the synthetic vitamin K.

Two conclusions may be drawn from this series of observations: (1) that vitamin K can be given intravenously to newborn babies with no untoward effect; and (2) that intravenous vitamin K rapidly lowers the prothrombin time and will control the bleeding of hemorrhagic disease of the newborn infant.

TABLE V

PATIENTS TREATED WITH INTRAVENOUS VITAMIN K

PATIENT	SITE OF BLEEDING	RESULT
1	Rectum, 4 to 6 hr.	Bleeding stopped; Hg., 104 per cent
2	External auditory meatus, 3 hr.	Bleeding stopped; Hg., 110 per cent
3	Into skin, 2 days	Bleeding stopped; transfusion later because Hg. 54 per cent
4	Bowel, 3 hr.	Bleeding stopped; transfusion later because Hg. 52 per cent
5	Intracranial, 2 days	Transfusion later; Hg., 60 per cent

Further data on the five cases which were treated with vitamin K are shown in Table V. In the first two, the bleeding was arrested with the hemoglobin at a normal level so no further treatment was necessary. In the other three, the hemoglobin measurements made shortly after admission reveal levels of 52, 54, and 60 per cent (Sahli), respectively. In these three cases, although the bleeding was arrested, they were handicapped by the low hemoglobin, and transfusion was given about twenty-four hours after admission. From a practical point of view, this is most important because, although one may arrest the bleeding with vitamin K, it is also necessary to restore the hemoglobin to a normal level.

One recommends, then, that a hemoglobin estimation be done when a patient with this disease is seen, and if the hemoglobin is decreased, that vitamin K be administered intravenously with a transfusion. If the hemoglobin is normal, give the vitamin K alone. In our experience to date, vitamin K with the transfusion does away with the necessity of second transfusions.

SUMMARY

Natural vitamin K may be given by mouth and synthetic vitamin K intravenously as well with no ill effects to patients of all ages.

The cord blood prothrombin time is prolonged in a large percentage of newborn infants, and this may be present without any clinical bleeding.

Daily administration of synthetic vitamin K by mouth to mothers for from two to sixteen days before delivery had no effect on their prothrombin time, but produced a shorter prothrombin time on the cord blood. This administration is recommended as a preventive measure for hemorrhagic disease.

The prothrombin time in cases of hemorrhagic disease of the newborn infant is prolonged and with the arrest of bleeding is materially shortened.

Vitamin K by mouth may not be retained or absorbed, so it is not safe to use this as a sole source of treatment.

Intravenous synthetic vitamin K will lower the prothrombin time and arrest bleeding in hemorrhagic disease of the newborn infant. If the hemoglobin is low, transfusion should be used in addition.

We wish to express our appreciation to Dr. R. W. Wesley of the Toronto Western Hospital and to his staff for their cooperation in this study.

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CONCENTRATION OF ASCORBIC ACID IN THE PLASMA DURING THE TREATMENT OF INFANTILE SCURVY

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THE PURPOSE of this paper is to present evidence of some of the changes that may occur in the plasma ascorbic acid concentration during the healing of infantile scurvy and to point out the inadequacy of the ascorbic acid level in plasma as an index of the nutritional state with respect to vitamin C.

Three patients who had symptomatic scurvy with pathognomonic, clinical, and characteristic roentgenographic signs were studied. They were fed pasteurized milk, small amounts of cooked vegetables, and cereal containing negligible amounts of ascorbic acid. Oleum percomorphum was the source of vitamin D. Samples of blood were obtained immediately before and three hours after* the administration of the single daily dose of ascorbic acid† which was usually given with the 9 A.M. feeding. Plasma ascorbic acid determinations were done by the microprocedure of Mindlin and Butler[3] without the addition of potassium cyanide to the collection tubes.[4, 5, 6] In Cases 1 and 2 the urine was collected for five hours after the ascorbic acid had been given, and its concentration therein was determined by a modification of the procedure of Evelyn, Malloy, and Rosen.[7]

The results are presented in the charts. Chart 1 demonstrates the course of the plasma ascorbic acid during the healing of scurvy in a patient treated with single, large daily doses of ascorbic acid until significant excretion of reducing substances occurred in the urine, and then by single daily doses of 25 mg. for an additional week. At first there was no increase in the plasma concentration with the ingestion of ascorbic acid. With repeated daily doses of 200 mg. of ascorbic acid the plasma concentration rose by steps so that after the seventh dose the renal threshold was exceeded. Thereafter, the patient was given the daily supplement of 25 mg. of ascorbic acid. The plasma concentration fell in three days from 1.4 to 1.0 mg. per cent, where it remained for the next four days. At the end of one week of the smaller dosage, the original large daily dose of ascorbic acid produced the same response in the blood plasma and in the urine that it had before. Failure of the ascorbic acid level in the plasma to rise after the ingestion of a large

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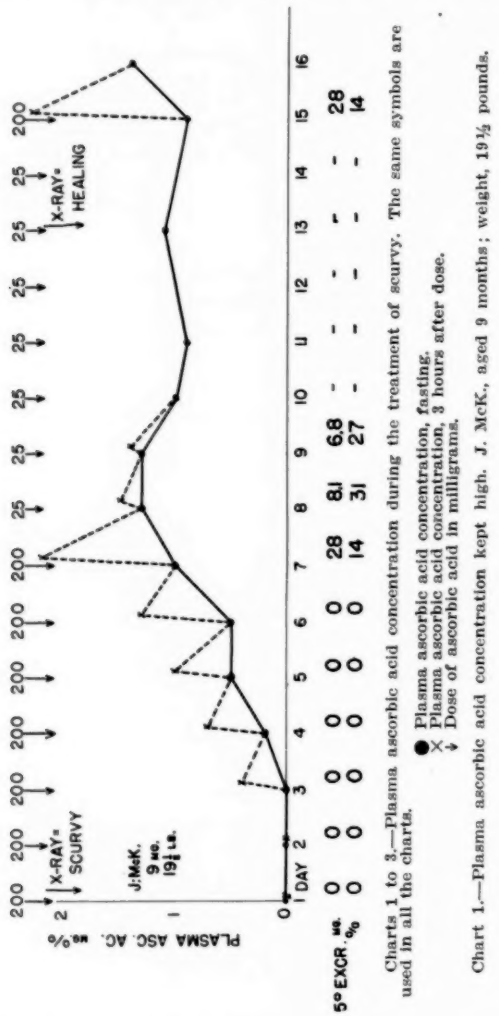
*It has been shown that the peak of the absorption curve of ascorbic acid following the ingestion of a single, large test dose comes in from 2 to 4 hours.[1, 2]

†The ascorbic acid was supplied by Merck and Company, Rahway, N. J.

amount of ascorbic acid is the usual finding in severe unsaturation, although it has been seen also in normal infants without clinical or roentgenographic evidence of scurvy who had been on deficient diets for several months. The same flat curve obtains in patients with deficient



Charts 1 to 3.—Plasma ascorbic acid concentration during the treatment of scurvy. The same symbols are used in all the charts.

● Plasma ascorbic acid concentration, fasting.
×→ Plasma ascorbic acid concentration, 3 hours after dose.
→ Dose of ascorbic acid in milligrams.

Chart 1.—Plasma ascorbic acid concentration kept high. J. McK., aged 9 months; weight, 19½ pounds.

absorption from the gastrointestinal tract from any cause; for example, this phenomenon has been observed in celiac disease without evidence of vitamin C deficiency. At the end of the period of observation the abrupt rise in the plasma concentration at three hours, the high fasting level at twenty-four hours, and the excretion of significant ascorbic acid in the

urine following the ingestion of 200 mg. of ascorbic acid indicated adequate tissue saturation.

In patient R. C. (Case 2) the clinical and roentgenographic signs were less marked. The response in the plasma to large daily doses, in this instance 175 mg., of ascorbic acid was, accordingly, more rapid. When significant excretion of ascorbic acid occurred in the urine, this patient was given 12.5 mg. of ascorbic acid daily for one week. The plasma ascorbic acid concentration fell at the end of five days to 0.2 to 0.3 mg. per cent. However, a single large dose of ascorbic acid at the end of the week again resulted in a prompt rise in the fasting plasma level and some excretion in the urine of the test dose. It is of interest that the ascorbic acid reserves in this patient remained constant, as measured by these criteria, during the interval that he received only 12.5 mg. of ascorbic acid daily.

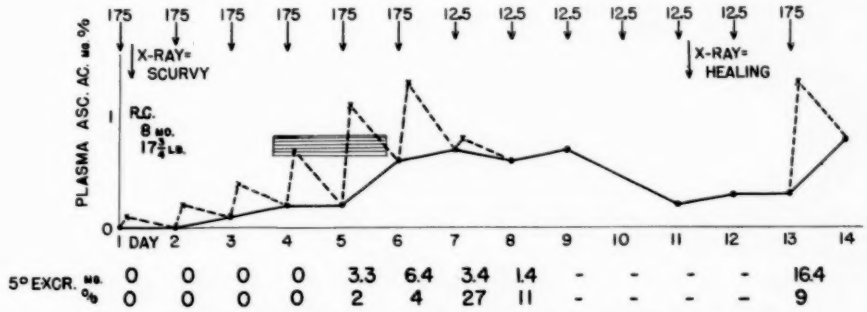


Chart 2.—Plasma ascorbic acid concentration allowed to become low. R. C., aged 8 months; weight, 17¾ pounds. The shaded area represents a mild febrile episode associated with upper respiratory infection.

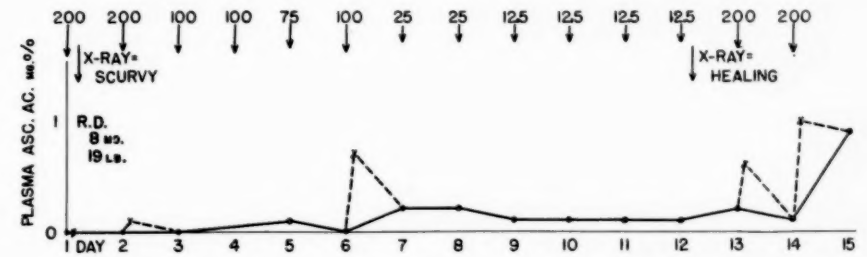


Chart 3.—Plasma ascorbic acid concentration kept low. R. D., aged 8 months; weight, 19 pounds.

The treatment of patient R. D. (Case 3) was designed to keep the plasma ascorbic acid concentration low. On the sixth day of treatment 100 mg. of ascorbic acid resulted in a rise in the plasma level at three hours to 0.8 mg. per cent and at twenty-four hours to 0.2 mg. per cent. Accordingly, he was given 25 mg. daily for the next two days, and when

the plasma ascorbic acid concentration remained at 0.2 mg. per cent, the dose was dropped to 12.5 mg. daily. There was then a fall in the plasma level to 0.1 mg. per cent, where it remained. After thirteen days of treatment the patient was given daily doses of 200 mg. of ascorbic acid. The fasting plasma level did not rise until after the second dose; this indicated that some unsaturation of the tissues was present. It is noteworthy, however, that the plasma ascorbic acid concentration prior to the dose which resulted in a rise in the fasting level was only 0.1 mg. per cent.

These three patients were symptom-free within forty-eight hours of the beginning of treatment, and roentgenographic evidences of healing were demonstrable in eleven to thirteen days despite the fact that there were wide differences in the ascorbic acid concentrations in their plasmas.

It has been demonstrated previously that in the newborn infant who receives no ascorbic acid the plasma ascorbic acid concentration falls to a very low level within two weeks.[8] Furthermore, if the infant is maintained on a scorbutogenic diet, the plasma ascorbic acid concentration remains low, and yet detectable clinical and roentgenographic evidences of scurvy do not make their appearance for several months.[2] Crandon and Lund[9] have followed the depletion of ascorbic acid reserves in a normal adult who was without diagnostic physical signs or symptoms and who showed normal wound healing after eighty-five days on a scorbutogenic diet when the plasma level had been below 0.2 mg. per cent for seventy days. Butler and Cushman[10] have demonstrated that the plasma ascorbic acid concentration falls to low levels long before there is an appreciable fall in the apparent ascorbic acid concentration of the white cell-platelet fraction of blood which is, presumably, a more accurate index of tissue saturation; during the treatment of scurvy the white cell-platelet ascorbic acid content increases before there is a rise in the plasma level. The data presented above indicate that scurvy can be cured regardless of the plasma ascorbic acid concentration and that an infant can be close to "saturation*" with a plasma level of 0.1 mg. per cent.

From the evidence reported herein and that available in the literature, the following statement may be made regarding the plasma ascorbic acid: A single, high fasting value indicates adequate ascorbic acid nutrition; a single, low fasting value indicates absence of ascorbic acid saturation, but not how far removed saturation may be; it has little value in the precise measurement of ascorbic acid undernutrition. Such measurement is better made by the determination of the ascorbic acid content

*"Saturation" is defined as the state of the organism when the ingestion of a large dose of ascorbic acid results in the excretion in the urine of a considerable fraction of the test dose. It has been found that a rise in the fasting level of ascorbic acid in the plasma regularly precedes, by only one or two doses, ascorbic acid excretion.

of whole blood,[11] the white cell-platelet fraction of blood,[10] or the plasma concentration responses to parenterally administered test doses of ascorbic acid.[12, 13]

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INTRACUTANEOUS VACCINATION AGAINST SMALLPOX BY MEANS OF THE CHICK EMBRYO CULTURE VIRUS

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INTRODUCTION

THE METHOD of obtaining cowpox vaccine virus for protective smallpox inoculation is essentially the same today as in Jenner's day (1796) except for steps taken to insure against contamination of the virus.

It had been recognized for years that the ideal virus for use in humans would be one cultivated in vitro in a pure state. It remained for Steinhardt, Israeli, and Lambert[1] in 1913 to devise a method for growing the virus in living tissue cells embedded in plasma on cover slips. This method, however, did not lend itself to adaptation for prophylactic measures against smallpox.

In 1915 Noguchi[2] obtained pure cultures of the vaccine virus by growth in rabbit testicle after having previously passed the virus through several generations of rabbits. Carrel and Rivers[3] in 1927 were the first to show that the vaccine virus could be made to grow in flasks containing bits of viable chick embryo in plasma. Then Maitland and Maitland[4] the following year showed that plasma was not necessary for the growth of the cultured virus.

In 1930 Li and Rivers[5] reported a method for the cultivation in vitro of a virus in a medium consisting of bacteria-free minced chick embryo suspended in Tyrode's solution. The next year Rivers[6] succeeded in adapting a dermal strain of New York City Department of Health cowpox virus to this method of cultivation and successfully vaccinated several children with the culture virus. Children thus vaccinated were found on revaccination to be refractory to standard calf lymph virus.

Since the culture virus was free from contaminating bacteria and in view of the mild character of the "takes," Rivers and Ward[7], by means of intracutaneous inoculation, vaccinated twenty-nine infants and children against smallpox with the culture virus. These children showed reactions interpreted as "primary takes" although these reactions were not accompanied by the formation of vesicles, pustules, or scars, and those tested later were found to be refractory to standard cowpox virus. In an effort to improve the keeping qualities of this new culture

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virus these same workers devised a method of preserving the virus by mixing it with sterile acacia and drying the mixture while in a frozen state. This method of preservation and storage does not lend itself to ready use by the average practitioner and pediatrician. The dried virus must be properly diluted just before use, and when once diluted does not retain its potency for more than 12 to 24 hours. Therefore it was desirable to make a preparation of the chick embryo virus which was properly diluted for use and so prepared that it would retain its potency for several months when stored in the ordinary refrigerators.

This study was conducted in the Prophylaxis Clinic of the Children's Medical Service of Bellevue Hospital from 1936 through 1939. Our clinical material was drawn from the poorer crowded tenement districts of New York City. All races, colors, and creeds were well represented. Infants and children from ages of 6 months to 5 years constituted the majority of our patients. However, some older children and even adults were followed for comparison and study.

The purpose was to study the clinical reactions noted following intracutaneous inoculation of the human by means of the chick embryo vaccine virus and to determine whether or not this culture virus is capable of producing immunity to smallpox as evidenced by cutaneous reactions of immunity upon subsequent revaccination dermally with a potent standard cowpox.

The chick embryo culture virus used in this study was prepared (at the Lederle Laboratories by Miss Louise Heaton, who also performed the rabbit potency tests) from a wet culture of vaccine virus obtained from Dr. Rivers. The virus originated as a calf lymph obtained from the New York City Department of Health.

The virus is inoculated into a medium consisting of minced fresh 11-day-old chick embryo tissue suspended in Tyrode's solution and placed in pyrex Blake bottles. It is then incubated for three days at 37° C. Virus, when ready for harvest, is smeared and examined for presence of contaminating organisms. Virus from noncontaminated bottles is pooled, sterility tested, and then sampled for rabbit skin tests.

If sterility tests are satisfactory, the lot of virus is ground through fine, sterile bolting silk to break up tissue particles. Then it is mixed with an equal volume of sterile inactivated human blood serum obtained from vaccinated and nonvaccinated donors who showed negative tests for syphilis. Finally it is preserved with two volumes of Kahbaum's bidistilled glycerine and placed in 5 c.c. rubberstoppered vials, and the potency is tested on the rabbit's skin.

The technique of human vaccination requires the use of a 1 c.c. all glass syringe graduated in tenths and a 27 gauge needle, $\frac{3}{8}$ inch in length. Needle and syringe were sterilized by boiling (and never used for any other purpose). For the sake of uniformity of results, the slightly depressed skin area over the insertion of the deltoid muscle

was selected for the site of injection. This area was cleansed with acetone solution and allowed to dry. The top of the ampule of virus solution was also sterilized with acetone solution and allowed to dry.

An intracutaneous injection of 0.1 c.c. of chick embryo culture virus is made into the prepared skin area in the same manner as in the Schick test. The injection must be given slowly because the material is quite viscid. If the injection is properly performed, a white, slightly elevated wheal with a small surrounding zone of erythema will be noted. After the injection has been completed and the needle withdrawn, it is important to cleanse the surface needle wound thoroughly with acetone in order to kill any virus which may escape from the puncture wound and cause the formation of a superficial surface vesicle and its subsequent scar. No dressing is applied, and the mother is instructed that the child may be bathed as usual.

Our first problem was to familiarize ourselves with the reactions which occurred after intracutaneous vaccination with the culture virus and compare the reactions with those obtained after vaccination by scarification with the usual calf virus.

A group of infants and children never before vaccinated were simultaneously vaccinated, on one arm with New York City Department of Health calf virus (scratch method), and on the other arm intracutaneously with 0.1 c.c. culture virus. These patients were seen daily, and the reactions studied. We were thus able to note the evolution of these two lesions simultaneously in the same individual. The intracutaneous lesion was found to follow a very definite pattern—just as definite as the cycle followed by dermal vaccination. The reactions ran through a very similar course as far as commencement, height of reaction, and subsidence of reactions were concerned, but the lesions produced were greatly different.

Another group of individuals never before vaccinated were given intracutaneous injections of 0.1 c.c. of chick embryo virus. They too were seen daily, and the reactions carefully noted. It was found that the lesions produced were identical with the lesions produced by intracutaneous vaccination on the group studied that had the simultaneous vaccination mentioned above. Thus the dermal calf virus vaccination done simultaneously did not affect the production of a typical intracutaneous lesion. (Similarly, individuals vaccinated with calf virus on different parts of the body at the same time, developed typical pock lesions at both sites.)

We next vaccinated intracutaneously a group of children with Rivers' dry virus in one arm and our wet culture virus in the other arm to study the reactions in the same individuals and to compare the clinical findings. We made all observations ourselves in order to obtain constant personal factors of evaluation.

A group of infants and children never before vaccinated and having a negative history for smallpox were given intracutaneous vaccination with culture virus prepared in slightly different manners. The patients were seen again at frequent intervals, usually two or three days later, then on the seventh to tenth day, and again after the fourteenth and the twenty-first days. Subsequent visits were made to the clinic thereafter at one- or two-month intervals. At each visit the reactions were carefully noted and recorded. The presence of systemic reactions, lymphadenopathy, and particularly the local manifestations were observed. The local reactions and the amount of erythema, swelling, and induration were carefully measured.

CHARACTERISTICS OF THE PRIMARY TAKE

The primary "take" following intracutaneous smallpox vaccination with the chick embryo virus is quite different from that following vaccination by the usual scarification, or pressure, or puncture methods with calf virus. No vesicle, no open sore, and no scar result. Instead, the following sequence of the reactions will be observed.

The blanched wheal resulting from the injection disappears in about twelve hours, leaving only a healing needle puncture wound. At the end of 24 to 48 hours there appears a small area of erythema with underlying induration of the same size. The area of erythema and induration gradually becomes larger until on the seventh day the erythematous zone has reached a size of 15 to 30 mm. in diameter. This is surmounted by a centrally located raised papule 6 to 8 mm. in size. There will also be noted at this time an area of underlying deeper induration, about 25 mm. in diameter, with a "shotty" feel. The height of the reaction is reached on the seventh to tenth day, at which time the local lesion is slightly larger. It then gradually diminishes in size so that on the fourteenth day there is present an area of faded erythematous pigmentation with slight superficial desquamation. Surmounting this pigmentation is a minute elevated papule, and there is also an area of underlying deep induration. The pigmentation and induration gradually become smaller and fade away completedly by the end of three to six weeks. However, a minute area of pigmentation and deep induration may persist for several months. Occasionally, at the height of the reaction a minute pin-point sized vesicle may be found. This is shortly replaced by a small scab which desquamates leaving no residue.

At the time of vaccination the patient usually complains of a stinging sensation at the site of injection. This is soon replaced by a slight itching which may persist for several days. At the height of the reaction the patient may be slightly irritable and suffer from mild malaise. The temperature rarely exceeds 100.4° F. Lymphadenopathy is rarely

present and is never troublesome. Over 90 per cent of vaccinated patients may be expected to escape all systemic reactions.

The above mentioned clinical findings after intracutaneous vaccination with chick embryo virus may be regarded as typical, having been carefully observed in over 800 vaccinations. There will be slight variations of the reactions depending upon the age of the patient, the amount of the skin pigmentation, and the site of the injection.

We next inoculated a group of infants and children with 0.1 c.c. of a control solution. This material was identical with our culture virus solution except that no virus was present. Also, these children were seen at regular intervals and the reactions noted, thus permitting us to know exactly how much of our local reaction was due to the diluent. The reactions were so slight in character that they could not possibly be confused with a typical "take."

When our observations were completed, the parent was given a certificate of vaccination which bore on it an expiration date varying from three months to three years. At the termination of this period the patient was then revaccinated dermally by the scratch method with a potent preparation of standard calf lymph virus (New York City Department of Health cowpox virus). The parent was cautioned about trauma, bathing, etc., and instructed to return with the patient in 24 to 48 hours. At this time observations of reactions were noted, and the patient again seen on the seventh, fourteenth, and twenty-first days so that the subsequent reactions could be studied.

The reactions following dermal cowpox revaccination were then classified into the following generally accepted reaction types.[8]

A. *Primary Take or Vaccinia* (indicating absence of immunity to smallpox). First to second day, wound heals; third to fourth day, small macule appears which quickly changes to a vesicle which covers the vaccinated area. This reaches maximum size by the seventh to ninth day and is surrounded by an area of erythema which reaches its maximum size of 1½ to 3 inches by the eighth to fourteenth day; the underlying and surrounding tissues are indurated. There is usually regional lymphadenopathy and some systemic reaction. By the tenth to eleventh day desiccation starts in the central umbilicated portion of the pock, and erythema starts to fade rapidly. Central drying of the pock continues until a scab is completely formed. This dries completely and usually falls off by the twenty-first day, leaving a reddened, depressed scar which gradually fades so that at the end of one to three months the characteristic white pitted scar is left.

B. *Accelerated Take or Vaccinoid* (indicating partial immunity to smallpox obtained from previous vaccination). Here the same process takes place, but it does so more rapidly. By the third to sixth day the vesicle with its surrounding zone of erythema and underlying induration has reached its height. On the ninth to tenth day the scab is

formed and falls off by the twelfth to fourteenth day, leaving a small scar which fades white in three to four weeks.

C. *Immune Reaction* (indicating full immunity, which occurs in those persons who have had smallpox or have immunity from previous vaccination). Here the area of erythema reaches its greatest size in eight to seventy-two hours. A papule may be formed but rarely a vesicle. The lesion fades completely in four to nine days, leaving no scar. Occasionally a small pinhead sized area of brownish pigmentation may remain.

D. *No Take.* This means *no vaccination* and does not indicate presence or absence of immunity to smallpox. This is due to faulty vaccination technique, or poor virus, or both. All children showing this reaction were immediately again vaccinated, and the resultant reactions noted.

To be certain that these reactions were typical for the potency of the calf virus used for revaccinations, several hundred children never before vaccinated were dermally vaccinated with Department of Health cowpox virus and their reactions studied. It was found that the primary takes encountered were absolutely identical with the reactions described by Leake.[8] We were therefore certain that our virus had the same potency as that required according to Leake's dictates, and thus our interpretation of *immune* and *accelerated* takes were accurate. Thus we were able to determine the degree of immunity (as measured by cowpox revaccination) which resulted from the original intracutaneous vaccination with the chick embryo culture virus.

RESULTS

The children who were given the culture virus were divided into several experimental groups for the purpose of comparison and evaluation. Of over 800 infants and children intracutaneously vaccinated against smallpox with culture virus, we were able to complete follow-up observations after dermal revaccination with Department of Health cowpox on only 290.

Group I consisted of 102 infants and children who were initially vaccinated intracutaneously with 0.1 c.c. of the culture virus which was mixed with blood serum obtained from human beings who had been previously vaccinated against smallpox. Of this group of children, 34 were initially vaccinated with a freezer specimen of the culture virus which had been grown for many generations by flask culture (Table I). Another group of children were intracutaneously vaccinated with a specimen of the culture virus which had been artificially "aged" by incubating for one week in an effort to determine if the properties were destroyed by storage out of a refrigerator. The figures are shown in Table II. The last group of 23 children were initially vaccinated with culture virus mixture which was obtained from a newly "seeded" virus, and results are recorded in Table III.

TABLE I

(GROUP I.) RESULTS OF REVACCINATION WITH NEW YORK CITY DEPARTMENT OF HEALTH COWPOX VIRUS OF INFANTS AND CHILDREN PREVIOUSLY VACCINATED INTRACUTANEOUSLY WITH 0.1 C.C. OF CULTURE VIRUS (FREEZER SPECIMEN) MIXED WITH HUMAN BLOOD SERUM FROM PREVIOUSLY VACCINATED DONORS

TIME INTERVAL BETWEEN INTRACUTANEOUS PRIMARY VACCINATION AND SUBSEQUENT DERMAL COWPOX VACCINATION (MONTHS)	NO. OF CHILDREN REVACCINATED	PRIMARY TAKE		ACCELERATED TAKE		IMMUNE REACTION	
		NO.	%	NO.	%	NO.	%
1-3	2	2	100	--	--	--	--
3-6	6	1	16.7	2	33.3	3	50
6-12	11	4	36.4	6	54.5	1	9.1
12-18	12	4	33.3	7	58.4	1	8.3
18-24	1	--	--	1	100	--	--
24	2	1	50	1	50	--	--
Total	34	12	35.3	17	50	5	14.7

TABLE II

(GROUP I.) RESULTS OF REVACCINATION WITH NEW YORK CITY DEPARTMENT OF HEALTH COWPOX VIRUS OF INFANTS AND CHILDREN PREVIOUSLY VACCINATED INTRACUTANEOUSLY WITH 0.1 C.C. OF CULTURE VIRUS (ONE-WEEK INCUBATED SPECIMEN) MIXED WITH HUMAN BLOOD SERUM FROM PREVIOUSLY VACCINATED DONORS

TIME INTERVAL BETWEEN INTRACUTANEOUS PRIMARY VACCINATION AND SUBSEQUENT DERMAL COWPOX VACCINATION (MONTHS)	NO. OF CHILDREN REVACCINATED	PRIMARY TAKE		ACCELERATED TAKE		IMMUNE REACTION	
		NO.	%	NO.	%	NO.	%
1-3	4	1	25	3	75	--	--
3-6	6	2	33.3	3	50	1	16.7
6-12	13	4	30.7	7	53.8	2	15.4
12-18	17	5	29.4	8	47.1	4	23.5
18-24	5	2	40	3	60	--	--
24	--	--	--	--	--	--	--
Total	45	14	31.1	24	53.3	7	15.6

TABLE III

(GROUP I.) RESULTS OF REVACCINATION WITH NEW YORK CITY DEPARTMENT OF HEALTH COWPOX VIRUS OF INFANTS AND CHILDREN PREVIOUSLY VACCINATED INTRACUTANEOUSLY WITH 0.1 C.C. OF CULTURE VIRUS (FREEZER SPECIMEN) MIXED WITH HUMAN BLOOD SERUM FROM PREVIOUSLY VACCINATED DONORS

TIME INTERVAL BETWEEN INTRACUTANEOUS PRIMARY VACCINATION AND SUBSEQUENT DERMAL COWPOX VACCINATION (MONTHS)	NO. OF CHILDREN REVACCINATED	PRIMARY TAKE		ACCELERATED TAKE		IMMUNE REACTION	
		NO.	%	NO.	%	NO.	%
1-3	4	1	25	2	50	1	25
3-6	3	3	100	--	--	--	--
6-12	11	3	27.3	5	45.4	3	27.3
12-18	4	1	25	2	50	1	25
18-24	1	--	--	1	100	--	--
24	--	--	--	--	--	--	--
Total	23	8	34.8	10	43.5	5	21.7

All of these subgroups had the common factor of virus mixed with blood serum from previously vaccinated donors. It is evident after a brief glance at Tables I, II, and III that the percentages of primary, accelerated, and immune reactions were essentially the same after revaccination with cowpox. The newly seeded virus gave a slightly higher percentage of immune reactions; this was to be expected. We shall now group together these 102 cases of infants and children initially vaccinated with culture virus mixed with serum from vaccinated donors and note the results of dermal revaccinations as shown in Table IV. These revaccinations were done at intervals of from one month to twenty-four months after the original immunization by means of culture virus. Thirty-four patients (or 33.3 per cent) reacted with primary takes. Fifty-one (or 50 per cent) reacted by giving accelerated takes while 17 (or 16.7 per cent) responded with immune reactions. It will further be noted that no immune reactions were obtained eighteen months after initial vaccination.

TABLE IV

(GROUP I.) RESULTS OF REVACCINATION WITH NEW YORK CITY DEPARTMENT OF HEALTH COWPOX VIRUS OF INFANTS AND CHILDREN PREVIOUSLY VACCINATED INTRACUTANEOUSLY WITH 0.1 C.C. OF CULTURE VIRUS MIXED WITH HUMAN BLOOD SERUM FROM PREVIOUSLY VACCINATED DONORS

TIME INTERVAL BETWEEN INTRACUTANEOUS PRIMARY VACCINATION AND SUBSEQUENT DERMAL COWPOX VACCINATION (MONTHS)	NO. OF CHILDREN REVACCINATED	PRIMARY TAKE		ACCELERATED TAKE		IMMUNE REACTION	
		NO.	%	NO.	%	NO.	%
1-3	10	4	40	5	50	1	10
3-6	15	6	40	5	33.3	4	26.7
6-12	35	11	31.4	18	51.4	6	17.2
12-18	33	10	30.3	17	51.5	6	18.2
18-24	7	2	28.5	5	71.5	--	--
24	2	1	50	1	50	--	--
Total	102	34	33.3	51	50	17	16.7

Group II of our children consisted of those individuals initially vaccinated intracutaneously with 0.1 c.c. of a culture virus, freshly seeded, which was mixed with glycerine and human blood serum from nonvaccinated donors (freezer specimen). In this group of 137 children results of revaccinations with Department of Health cowpox virus dermally administered is shown in Table V. We find that of the 137 children, a total of 14 (or 10.2 per cent) responded with primary takes. There were 96 (or 70.1 per cent) children who gave accelerated reactions. Immune reactions were encountered in 27 (or 19.7 per cent) children.

The only essential difference between the virus used in Group I and that used in Group II is that blood serum from previously vaccinated donors was used in Group I and from nonvaccinated donors in Group II. The results in Group II were superior, as shown by the decidedly smaller number of primary takes, a drop from 33.3 per cent to 10.2 per cent.

TABLE V

(GROUP II.) RESULTS OF REVACCINATION WITH NEW YORK CITY DEPARTMENT OF HEALTH COWPOX VIRUS OF INFANTS AND CHILDREN PREVIOUSLY VACCINATED INTRACUTANEOUSLY WITH 0.1 C.C. OF CULTURE VIRUS (FREEZER SPECIMEN) MIXED WITH HUMAN BLOOD SERUM FROM NONVACCINATED DONORS

TIME INTERVAL BETWEEN INTRACUTANEOUS PRIMARY VACCINATION AND SUBSEQUENT DERMAL COWPOX VACCINATION (MONTHS)	NO. OF CHILDREN REVACCINATED	PRIMARY TAKE		ACCELERATED TAKE		IMMUNE REACTION	
		NO.	%	NO.	%	NO.	%
1-3	3	--	--	--	--	3	100
3-6	9	2	22.2	7	77.8	--	--
6-12	83	8	9.6	59	71.1	16	19.3
12-18	29	2	6.9	22	75.8	5	17.3
18-24	13	2	15.4	8	61.5	3	23.1
24	--	--	--	--	--	--	--
Total	137	14	10.2	96	70.1	27	19.7

TABLE VI

(GROUP III.) RESULTS OF REVACCINATION WITH NEW YORK CITY DEPARTMENT OF HEALTH COWPOX VIRUS OF INFANTS AND CHILDREN PREVIOUSLY VACCINATED INTRACUTANEOUSLY SIMULTANEOUSLY WITH 0.1 C.C. OF CULTURE VIRUS (FREEZER SPECIMEN) AND 0.1 C.C. OF CULTURE VIRUS (ONE-WEEK INCUBATED SPECIMEN) MIXED WITH HUMAN BLOOD SERUM FROM NONVACCINATED DONORS (NEW VIRUS)

TIME INTERVAL BETWEEN INTRACUTANEOUS PRIMARY VACCINATION AND SUBSEQUENT DERMAL COWPOX VACCINATION (MONTHS)	NO. OF CHILDREN REVACCINATED	PRIMARY TAKE		ACCELERATED TAKE		IMMUNE REACTION	
		NO.	%	NO.	%	NO.	%
1-3	--	--	--	--	--	--	--
3-6	--	--	--	--	--	--	--
6-12	10	--	--	5	50	5	50
12-18	5	--	--	3	60	2	40
18-24	6	1	16.7	2	33.3	3	50
24	1	--	--	--	--	1	100
Total	22	1	4.5	10	45.5	11	50

TABLE VII

(GROUP III.) RESULTS OF REVACCINATION WITH NEW YORK CITY DEPARTMENT OF HEALTH COWPOX VIRUS OF INFANTS AND CHILDREN PREVIOUSLY VACCINATED SIMULTANEOUSLY INTRACUTANEOUSLY WITH 0.1 C.C. OF CULTURE VIRUS (FREEZER SPECIMEN) MIXED WITH HUMAN BLOOD SERUM FROM NONVACCINATED DONORS, AND WITH 0.1 C.C. OF RIVERS' CULTURE VIRUS

TIME INTERVAL BETWEEN INTRACUTANEOUS PRIMARY VACCINATION AND SUBSEQUENT DERMAL COWPOX VACCINATION (MONTHS)	NO. OF CHILDREN REVACCINATED	PRIMARY TAKE		ACCELERATED TAKE		IMMUNE REACTION	
		NO.	%	NO.	%	NO.	%
1-3	--	--	--	--	--	--	--
3-6	--	--	--	--	--	--	--
6-12	5	--	--	4	80	1	20
12-18	2	--	--	--	--	2	100
18-24	7	--	--	5	71.5	2	28.5
24	6	1	16.7	3	50	2	33.3
Total	20	1	5	12	60	7	35

It will be further noted that immune reactions were encountered at the end of twenty-four months in Group II; this indicated a more lasting immunity when nonvaccinated blood serum was used. This difference, we believe, is due to the presence of immune bodies in the blood serum from previously vaccinated donors which, when mixed with the culture virus, serve to neutralize it partially, or attenuate its activity.

It occurred to us that, since these intracutaneous vaccinations were so innocuous and caused so little discomfort to the patient, we might give two injections simultaneously on different sites of the body in order to introduce a greater amount of antigen and thus produce a better immunity. Therefore, the 42 infants and children in Group III were given vaccinations by means of two intracutaneous injections of 0.1 c.c. of culture virus in different parts of the body. This group was subdivided: Twenty-two individuals received 0.1 c.c. of culture virus, freezer specimen, in one arm and 0.1 c.c. of one-week incubated virus in the other arm; 20 children received 0.1 c.c. of culture virus, freezer specimen, mixed with blood serum from nonvaccinated donors in one arm and 0.1 c.c. of Rivers' (dry) virus in the other arm. The results of revaccination of these children are shown in Tables VI and VII. As will be noted the results are essentially the same with a slightly better immunity being shown in those receiving two injections of the wet virus. When we combine our results of these 42 children with simultaneous vaccination as shown in Table VIII, our results are quite striking. We find that 18 (or 42.9 per cent) have responded with immune reactions and that 22 (or 52.3 per cent) have given accelerated reactions. Thus, we obtained considerable immunity in over 95 per cent of the patients. Moreover, complete immunity was noted well over twenty-four months after original vaccination.

TABLE VIII

(GROUP III.) RESULTS OF REVACCINATION WITH NEW YORK CITY DEPARTMENT OF HEALTH COWPOX VIRUS OF INFANTS AND CHILDREN PREVIOUSLY VACCINATED SIMULTANEOUSLY INTRACUTANEOUSLY WITH TWO INJECTIONS OF 0.1 C.C. CULTURE VIRUS PURE OR MIXED WITH HUMAN BLOOD SERUM FROM NONVACCINATED DONORS

TIME INTERVAL BETWEEN INTRACUTANEOUS PRIMARY VACCINATION AND SUBSEQUENT DERMAL COWPOX VACCINATION (MONTHS)	NO. OF CHILDREN REVACCINATED	PRIMARY TAKE		ACCELERATED TAKE		IMMUNE REACTION	
		NO.	%	NO.	%	NO.	%
1-3	--	--	--	--	--	--	--
3-6	--	--	--	--	--	--	--
6-12	15	--	--	9	60	6	40
12-18	7	--	--	3	42.9	4	57.1
18-24	13	1	7.7	7	53.8	5	38.5
24	7	1	14.4	3	42.8	3	42.8
Total	42	2	4.8	22	52.3	18	42.9

DISCUSSION AND COMMENT

It has been generally accepted that vaccination of the newborn infant runs through a milder course than in the older infant or young children.

Donnally and Nicholson[9] in 1934 reported their results on vaccination in newborn infants and stated that reactions were much milder than in older children, but because of the resistance of growing young tissue to infection many were refractory to successful vaccination. They further noted that "some individuals lose their immunity to smallpox more rapidly than others, especially infants." This was further borne out by Nils Malmberg,[10] who reported that vaccination against smallpox in the first few weeks of life usually gave poor results and by Pinto,[11] who found that the immunity was not very lasting if primary vaccination was done on very young infants.

The individuals included in this study we are reporting were all over 6 months of age and did not exceed 5 years of age. Hence, we could assume that they were susceptible to vaccination and could develop immunity in a normal manner. We were impressed with the mildness of the local reactions and the almost complete absence of systemic reactions found with the typical primary take after intracutaneous vaccination with culture virus. This was particularly striking when compared with the reactions observed after dermal vaccination with New York City Department of Health cowpox virus.

Rivers, Ward, and Baird[12] recently reported on the revaccinations of 331 individuals originally vaccinated with culture virus and then revaccinated with New York City Department of Health cowpox virus. However, in their study only a single observation was made after revaccination. It was made on the fifth day in the majority of cases and on the fourth or seventh day in a few cases. Therefore it was impossible for them to classify the results of revaccination according to the standard accepted criteria of Leake.[8] Undoubtedly the results they report would be somewhat altered if more frequent observations had been made. Also, some of their revaccinations were done with commercial cowpox virus of much less potency than the New York City Department of Health cowpox virus.

Ellis and Boynton[13] have reported vaccinations with Rivers' virus on a group of 3,000 college students. Unfortunately, however, they were only able to complete observations on 90 individuals. The vaccination with the intradermal virus was made on the flexor surface of the forearm. They encountered constitutional reactions in 20 per cent of the cases and noted the formation of scars in 70 per cent of the individuals. We found results which are greatly different from theirs and which can only be explained by a difference in technique and by the fact that they were working with an older age group. Only rarely did we encounter systemic reactions, in less than 1 per cent of the cases; scar formation was noted in 11 per cent of children injected with the modified culture virus and in 38 per cent of those given Rivers' virus; and the average size of the resultant scar was only 2 mm. by 3 mm.

Ellis and Boynton further emphasize that the only reliable clinical method of determining immunity to smallpox is by revaccinating with

a potent strain of vaccine virus and then classifying reactions according to the criteria of Leake. They did not have the opportunity to do this in the cases studied.

The most recently published work on vaccination with the culture virus was by Donnally[14] who reported on a series of 37 newborn infants successfully vaccinated with Rivers' virus and then after a lapse of 1 to 2 years revaccinated dermally with New York City Department of Health cowpox. He found that over 80 per cent of these 37 cases were found to have slight or no immunity. This is very definitely in accordance with his earlier observations, with which we concur, that newborn infants are resistant to infection with vaccine virus, and that immunity is lost most rapidly.

The literature is filled with reports on the duration of immunity to smallpox conferred by vaccination. The reports are so conflicting that proper evaluation is well-nigh impossible. The reason for these great differences probably lies in the fact that vaccine virus of different potency was used for initial vaccination and of varying potency for revaccination; thus proper interpretation cannot be made.

From the chaos of reports it is only fair to state that immunity lasts from two months to a lifetime and that a great deal of immunity is lost after 3 to 5 years. At this time, then, we cannot critically compare the degree and duration of immunity to smallpox stimulated by intracutaneous injection of the chick embryo culture virus with that obtained after dermal vaccination with cowpox. That comparison must await more carefully controlled studies.

CONCLUSIONS

Our results in this particular study indicate that immunity to smallpox as measured by dermal revaccination can be obtained in a high degree after the intracutaneous injection of 0.1 c.c. of chick embryo culture virus. Two injections give a still greater immunity. This culture virus is obtained by adapting the cowpox vaccine virus to growth on the chick embryo according to the method of Rivers. The harvested virus may be preserved by the use of glycerine and human blood serum and in such a wet state as is readily available for use.

The activity of the virus is diminished if the human serum with which it is mixed has come from previously vaccinated donors. The virus solution maintains its activity for several months when stored in a refrigerator and taken out for short periods of time when being used.

Vaccination intracutaneously with the culture virus may be done rapidly and efficiently by the average practicing physician. The reactions of primary vaccination are characteristic and may be readily recognized. The course of vaccination is benign. Systemic reactions are rare. A minute scar may result in a few individuals. Usually pustule formation with its subsequent vesiculation and scab do not occur. The objection to this method because it does not leave a scar is not valid,

since the presence of a scar does not indicate immunity to smallpox; it merely indicates that the individual has been previously vaccinated dermally with the vaccine virus.

We firmly believe that intracutaneous vaccination is the method of choice and suggest that after a lapse of about two years revaccination with culture virus or cowpox be made. Subsequent publications will report the reactions of immunity (immune) and of partial immunity (accelerated) obtained with the culture virus when injected into previously vaccinated individuals.

SUMMARY

1. Over 800 infants and children between the ages of six months and five years were intracutaneously vaccinated with a commercial preparation of the chick embryo culture virus.

2. A total of 290 of these children were dermally revaccinated with New York City Department of Health cowpox virus after a period of from six months to thirty months.

A. Of those initially vaccinated with 0.1 c.c. culture virus mixed with blood serum from nonimmune donors, there were 10.2 per cent per cent primary takes, 50 per cent accelerated takes, and 16.7 per cent immune reactions.

B. Of those originally vaccinated with 0.1 c.c. culture virus mixed with blood serum from non-immune donors, there were 10.2 per cent primary takes, 70.1 per cent accelerated takes, and 19.7 per cent immune reactions.

C. Of those initially vaccinated with two injections of 0.1 c.c. of culture virus, there were 4.8 per cent primary takes, 52.3 per cent accelerated takes, and 42.9 per cent immune reactions.

3. Immunity to smallpox as measured by refractoriness to cowpox may be obtained to a high degree with culture virus vaccination.

4. Two injections of 0.1 c.c. each of culture virus result in the highest degree of immunity.

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127 WEST 79 STREET

FORMOLIZED VACCINIA VIRUS

Results of Its Use With Children Who Had Never Been Vaccinated Previously

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THE occurrence of undesirable complications and sequelae of vaccination with calf lymph virus justifies the continued search for improvement in our methods of vaccination. The problem of establishing immunity to smallpox without severe cutaneous lesions and with as little discomfort as possible, with vaccinia virus free of bacteria and other viruses, still confronts workers in this field. The use of an inactivated virus for vaccination would offer many advantages because it would combine certain sterility with safety from the consequences of a possible propagation of virus.

Experience gained in the past with the immunizing effect of inactivated virus preparations gave little encouragement, either experimentally or clinically. As is the case in immunity against bacterial infection, immunization against viruses requires the introduction of an amount of virus sufficient for the stimulation of antibodies. In most of the virus diseases, organs of diseased animals are the only source of virus available. Very often the best suspensions obtainable do not contain virus enough to evoke appreciable antibody response.

A striking example of this is the case of equine encephalomyelitis. The culture of this virus on chick embryo (Beard, Finkelstein, Sealy, and Wyckoff[1]) made preparations available which were very rich in virus, and soon thereafter it was shown that suspensions made from chick embryos infected with equine encephalomyelitis virus and inactivated with formalin had an immunizing effect many times superior to suspensions of brain tissue which had been used theretofore (Eichhorn and Wyckoff[2]). The prophylactic effect in horses of such material has since been amply confirmed in the field (Mitchell, Walker, and Plummer[3]). Considerable formation of antibody was demonstrated also in human beings injected with formolized encephalitis virus (Beard, Beard, and Finkelstein[20]). It will be enough to recall a few further examples in which satisfactory evidence of the immunizing effect of inactivated virus preparations has been obtained: rabies (Semple[4]), distemper

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(Laidlaw and Dunkin[5]), and typhus fever (Zinsser and Castaneda,[6] and further literature by Zia, Pang, and Liu[7]).*

There is no reason to suppose that there is a fundamental difference between bacterial and viral infections in the reactions of the host. However, the biologic peculiarities of viruses and the effects of the differences in size (Merrill[10]) have to be duly considered.

The method described by Craigie[11] has made it possible to obtain suspensions of elementary bodies of vaccinal virus in ample amounts and of a considerable degree of purity. Such preparations were used by one of us[12] to take up once more the problem of the immunizing effect of inactivated vaccinal virus. Special attention was paid to the quantitative aspects of this problem. Purified suspensions of elementary bodies obtained according to Craigie's method were inactivated with formalin. It was found that suspensions of this kind evoked an immunity response in rabbits which could well be compared with that engendered by active virus in the same animal. The antibody titer in the serum was evaluated by complement fixation and neutralization tests in the skin of rabbits, and it was also determined what amounts of virus would be neutralized in the skin of the immunized animal.

It was found that quantities of elementary bodies weighing not less than one or more milligrams dry weight were necessary in order to obtain this effect. Quantitative data discussed by Weil and Gall[12] made it seem likely that the amounts of virus produced in the body† by vaccination with active virus may be comparable to the amounts of inactivated virus found necessary in order to evoke an immunity response with formolized vaccinal virus in the rabbit.

These experimental results encouraged us to try out the immunizing effect in human beings of elementary body suspensions inactivated by formalin. Suspensions of elementary bodies were prepared according to Craigie and inactivated by 0.25 per cent formalin. Inactivation was controlled by serial passages of the material both in rabbit testis and on the chorioallantoic membrane of chick embryos; in neither medium was a sign of active virus observed after inoculation of 20 mg. The virus suspensions were standardized by dry weight.

RESULTS OF ITS USE WITH CHILDREN

Children between the ages of 3 and 7 years, who had never been vaccinated previously, were selected for this study. Each child was given three intradermal inoculations of formolized vaccinia virus at weekly intervals. At varying periods after the first inoculation, the

*The evidence of the immunizing effect of rabies is based mostly on the experience in the field.[13, 14] Webster[8] has pointed out the gaps in the experimental proof, and it remains to be seen whether the mouse method[9] proposed by him will give more consistent results. In the case of distemper, the veterinarians infect the animals with virulent distemper virus when the initial immunity evoked by inactivated virus is at its highest point, in order to obtain a lasting immunity.

†Craigie cited by Tulloch[10] may here be quoted: "The living 'seed' virus introduced at vaccination proliferates enormously and it is the sum total of the progeny of the initial seed, both in the local lesion and disseminated throughout the body, which provides the antigenic stimulus—not the minute quantity of seed virus."

minimum being four weeks, the maximum seven weeks, they were vigorously vaccinated cutaneously with calf lymph virus from the New York City Bureau of Laboratories.

The first fifteen children each received a total of 0.021 mg. of inactivated virus prepared by one of us (A. J. W.) and standardized by dry weight of elementary bodies of vaccinia. The next two children each received a total of 1.11 mg., and the next child 2.01 mg.; the next child, No. 20, received 4.1 mg., child 22 received 2.1 mg. and child 23 received 3.0 mg. of formalinized vaccinia virus.

LOCAL REACTIONS

The three doses given to the first fifteen children were 0.001 mg. at the first inoculation, 0.01 mg. at the second, and 0.01 mg. at the third. The skin reactions were slight and negligible. The sites were not followed closely because these were outpatients, but the mothers were asked to keep a close watch and report upon the skin reactions following each inoculation. Every mother reported a trivial skin reaction or none at all, mostly the latter, following the doses mentioned just above.

When the intradermal dose of formalinized vaccinia virus amounted to 1.0 mg. or more, there was generally a reaction consisting of an erythematous nodule in the skin approximately 7 mm. in diameter. In no instance was regional lymphadenopathy observed. The nodule persisted for from two to four weeks or more, and was followed by a superficial pitting.

In No. 22, a boy 4½ years of age, the skin reaction following 0.1 mg. of formalinized vaccinia virus was a red area the size of a dime, which disappeared within twenty-four hours. A week later when he received an intradermal inoculation of 1.0 mg., there developed within a few hours a red area the size of a dime, and gradually a red nodule 7 by 6 mm. The following week 1.0 mg. caused a similar redness; eight hours later the mother described it as being the size of a twenty-five-cent piece, and it persisted on the second day. On the third day the red area was the size of a half-dollar. On the fifth, sixth, and seventh days a nodule, the size of a large pea, developed in the red area, and the nodule became flattened and enlarged, described to be "like a lima bean." This became capped with a vesicle. On the twelfth day there was crust formation, and on the thirteenth day the scab dropped off, leaving two small superficial depressions 3 by 2 mm. each. From the description, the skin reaction in this case seemed to resemble a "take" produced by a weak virus; it was probably not a vaccinal cycle.

Child 20, a white boy of 6½ years, received as his first intradermal inoculation 0.1 mg. of formalinized vaccinia virus. No redness or swelling occurred with this inoculation. A week later, his second intradermal inoculation of 1.0 mg. resulted in a red area the size of

a ten-cent piece, which remained for a day only, and he had a "sore arm" for two days. One week later he received a third intradermal inoculation of 3.0 mg. This was followed by a red area and nodule formation, which persisted for a month. He scratched the area when

Fig. 1.—*A*, Skin reaction to intradermal injection of formolized vaccine virus from the twenty-third to the twenty-ninth days.

Vaccination with active calf virus two weeks after the third inoculation of formolized vaccinia virus was unsuccessful. Revaccination eight days later with active calf virus was successful, with moderate skin reactions (*B*) on the second, third, seventh, and eighth days.

it itched and a scab formed. At the time of revaccination with active calf virus, it looked like a "take" which was drying up, produced by a weak vaccinia virus. The crust was 3 by 2 mm., and the nodule and redness were 10 by 7 mm. (Fig. 1). In this instance there was no definite resemblance to a vaccinal cycle.

Child 23, a boy of 5 years who received intradermally 1.0 mg. of formalinized vaccinia virus as his first inoculation, reacted negligibly in the skin. A week later 1.0 mg. produced redness the size of a dime. A week later a third inoculation of 1.0 mg. was followed by a red area and nodule 7 by 7 mm., which had little resemblance to a vaccinal cycle but resembled somewhat the peak of a "take" with a weak virus.

Child 17, a little white girl of 3 years, had negligible reactions to 0.01 mg. and to 0.1 mg. of formalinized vaccinia virus given one week later. Her third inoculation of 1.0 mg. intradermally was reported to have been followed neither by redness nor swelling.

ESTIMATE OF IMMUNITY DUE TO INTRADERMAL INOCULATION OF FORMOLIZED VACCINIA VIRUS

Two of the first fifteen children who had received a total of 0.021 mg. of formalinized vaccinia virus, upon vigorous vaccination with calf lymph virus, showed the following results: (1) an immune reaction in No. 3, a Chinese boy aged 4 years, and (2) no skin reaction whatever in No. 12, a white boy aged 4 years. The Chinese boy was revaccinated a week later with calf lymph virus cutaneously with 60 needle pressures, to which he responded by a severe "take."

Child 12, the white boy, was revaccinated five days later with calf lymph virus cutaneously with 60 needle pressures. The skin reaction to this revaccination was very marked. Scratching resulted in four marked "takes" by autoinoculation on his right leg. There was definite cellulitis over the groin glands, and a temperature of 104° F., and he spent the next four days in the Children's Hospital during the peak of his vaccinia.

Child 20, a boy 6½ years of age (see Fig. 1), who had received a total of 4.1 mg. of inactivated virus, had no skin reaction upon vaccination with calf lymph virus, 30 needle pressures cutaneously. He was observed for eight days and showed no signs of a "take." *Re*vaccination at the end of eight days with 50 needle pressures cutaneously showed a marked skin reaction, a successful "take."

Child 22, a white boy aged 4½ years, who had received a total of 2.1 mg. of inactivated virus, showed upon vaccination no visible skin reaction within the following week. At the end of the week he was *re*vaccinated cutaneously with 50 needle pressures and there resulted a moderate "take."

Child 23, a white boy aged 5 years, who had received a total of 3.0 mg. of formalinized vaccinia virus, upon vaccination with calf lymph virus cutaneously with 50 needle pressures, four weeks after his first inoculation with inactivated virus, had only a moderate "take."

Among the entire twenty-one children, four failed to respond by a "take" upon first insertion of calf lymph virus. All of these responded to revaccination a week later with a "take." The formalinized vaccinia virus produced apparently a partial immunity to vaccinia mani-

fested by four failures to get "takes" on first insertion of active calf virus. The resistance to successful vaccination was broken down by revaccination with the "hot virus" of the New York Bureau of Laboratories, inserted by 50 or 60 needle pressures cutaneously.

STUDY OF THE BLOOD SERUM OF THE CHILDREN

Specimens of blood were obtained from all of the children before the formolized vaccine virus was inoculated, and again four to seven weeks after the first inoculations, and two to five weeks after the third inoculations of it. These were used for controlled tests for the development of antibodies; these tests were further controlled by positive immune rabbit serum, and the serum of one of us (A. J. W.), which latter was found to fix complement in a dilution of 1:50, and in rabbits to neutralize 100 minimal reacting doses of calf lymph virus.

Complement Fixation.—All sera taken before and after the inoculation of formalinized vaccine virus were found to be negative, except that of No. 17. This child had been inoculated as follows:

Aug. 23, 1939:	Formolized vaccinia virus	0.01 mg. intradermally
Aug. 30, 1939:	Formolized vaccinia virus	0.10 mg. intradermally
Sept. 6, 1939:	Formolized vaccinia virus	1.00 mg. intradermally
	Total	1.11 mg.

Sept. 27, 1939: Positive complement fixation in a serum dilution of 1:20.

Neutralization tests were done in the skin of rabbits: the sera of children 12 and 13 before inoculation with formolized virus were negative. Serum from child 1, a little girl of 4 years, neutralized 100 minimal reacting doses of calf lymph virus in the skin of a rabbit. The details of her case were:

July 7, 1939:	Formolized vaccine virus	0.001 mg. intradermally
July 12, 1939:	Formolized vaccine virus	0.010 mg. intradermally
July 19, 1939:	Formolized vaccine virus	0.010 mg. intradermally
	Total	0.021 mg.

Aug. 23, 1939: Blood obtained, the serum of which neutralized 100 minimal reacting doses of calf virus.

Child 12 showed no antibodies before inoculation and none three and one-half weeks *after* inoculation with a total of 0.021 mg. of formolized vaccine virus. The record of this 4-year-old boy is repeated here. His first calf lymph virus inoculation with 30 needle pressures showed no skin reaction. Five days later he was revaccinated with 60 needle pressures and gentle rubbing of the site. He had marked skin reaction, multiple autoinoculation vaccination sites, a temperature of 104° F.,

and was sick for four days in the hospital. Four weeks after his *re*-vaccination, when all of the vaccination sites had healed, his blood serum neutralized 100 minimal reacting doses of calf lymph virus.

Sera from all of the other children were tested after attempted immunization with formalinized vaccine virus and were found to give negative neutralization tests with calf lymph virus in the skin of rabbits.

COMMENT

The use of formalinized vaccine virus in rabbits engendered an immune state in them, equal to the immune state resulting from infection with active calf virus, when the immune states are compared on the basis of circulating antibodies. But the best way in children to compare states of immunity to vaccinia, and probably to smallpox, is not by circulating antibodies, not by size of the initial skin reaction to vaccination, but by the response to revaccination with active calf virus. Henderson and McClean[15] attempted to detect changes in circulating antibody before and after vaccination in a small group of nurses. Some of these nurses showed slight increase fourteen days after vaccination, and others none at all; "but no correlation could be obtained between neutralization tests, the size of the initial, intracutaneous lesion, or the immunity to subsequent revaccination." In our study, child 1, who alone showed neutralizing antibodies in the blood serum after formolized vaccine virus only, was found to have a marked skin reaction to vaccination with active calf virus. The vesicle was 20 by 14 mm., and maximum areola formation 95 by 70 mm., which represents an unusually severe skin reaction to vaccination. Child 17 alone showed complement fixation in a serum dilution of 1:20; upon vaccination with active calf virus she had an average or moderate skin reaction, a vesicle 10 by 10 mm., and a moderate sized areola 30 by 30 mm.

The hot calf virus used in our study has been shown (Donnally, Nicholson, Anderson, and Grosvenor[16]) to result in "takes" in 93 per cent of children, whether inoculated cutaneously or intradermally; i.e., in carefully performed vaccinations about one in fifteen children fails to have a successful "take" on the first insertion. In the first fifteen children, each of whom received a total of 0.021 mg. of formalinized vaccine virus, only one failed to take on first vaccination with calf virus, and in this one revaccination was successful.

Among the next six children, who each received from 1.11 to 4.1 mg. of formolized vaccine virus, two (33 per cent) of them failed to have successful "takes" on the first insertion of active calf virus. This contrasts with an expected failure on first insertion of 7 per cent, and this indicated to us that formalinized vaccine virus resulted in a definite something which made vaccination more difficult. This something we regard as partial immunity.

One of us (H. H. D.) performed the vaccinations of the children with active virus and did so with a drop of calf lymph on the dry skin with from 15 to 60 needle pressures by Leake's method.[17] This is severe technique. It may be open to the objection that the method was too severe and might result in a "take" even though there was sufficient immunity to smallpox to prevent infection. Newborn infants vaccinated within two or three days after birth with active calf virus showed after two to three years, upon *re*vaccination[18] by the same technique, good immunity in 73.5 per cent, including immune reactions in 32.3 per cent. These results, we think, justify the technique of revaccination employed.

The skin reaction to the third inoculation of 1.0 mg. or more of formolized vaccine virus usually consisted of a nodule 7 mm. in diameter surrounded by a small area of redness. These nodules persisted for from two to four weeks and were followed usually by crusting with superficial pitting as the crust dropped off. They resembled a "take" with a weak virus, but there was no definite vaccinal cycle. A mild skin reaction with active calf virus was not much more objectionable.

The partial immunity which resulted was not solid or durable, but readily broken through to yield a definite Jennerian vesicle, following insertion of active calf virus. Further study and modifications of technique of preparation and insertion of the formolized vaccine virus may be able to overcome these objections. Henderson and McClean[15] stress the importance of vesiculation in the production of immunity.

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ROCKY MOUNTAIN SPOTTED FEVER

An Analysis of Eighteen Cases in Children

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ROCKY MOUNTAIN spotted fever has long been recognized in the western section of the United States, but it was not until 1930 that the disease was identified in the eastern section of our country. Included among the early cases studied in the Atlantic States was a patient admitted to the Children's Hospital, Washington, D. C., in 1930. The story of this child is a most interesting one.

The boy, aged 9 years, entered the hospital on the third day of his illness. From the onset he had been feverish, restless, and irritable, and complained of headache and stomach-ache. On the day of admission to the hospital he vomited. The physical examination revealed acute abdominal tenderness on the right side with slight rigidity of the right rectus muscle. The leucocyte count was 11,950 with 94 per cent polymorphonuclears. A diagnosis of acute appendicitis was made from the history and physical findings. His appendix was removed, and the pathologic report was:

"Probably chronic and subacute appendicitis."

The following day, the fourth day of his illness, the patient was quite toxic and presented signs of meningeal irritation. A lumbar puncture was done; there was no increase in pressure of the cerebrospinal fluid; and examination of the fluid was normal. A blood culture was taken on this day, but no growth was ever obtained. On the fifth day the child was very toxic. The clinical impression was typhoid fever with meningismus. In the afternoon of this day there appeared a skin eruption which was first noticed on the chest and arms and was described as a discrete, macular, purplish-red rash, which disappeared almost completely, but not entirely so, on pressure. Another spinal puncture was done to exclude meningococcus meningitis. The fluid again obtained was reported to be normal. The rash, together with the high fever and marked toxicity, aroused the suspicion that the illness might belong to the typhus group. Death occurred on the ninth day of the disease.

Since this time there have been 17 cases of Rocky Mountain spotted fever admitted to Children's Hospital, making a total of 18 cases in the past nine years. We are prompted to present an analysis of these 18 cases in order to draw a clinical picture of the disease as it occurs in childhood, since the literature on this disease in children is meager.

The first case in our series was admitted to the hospital in September, 1930, and the last in July, 1939. All of the cases were admitted in the spring and summer months, or during the season when ticks are most numerous. Fourteen out of 18 cases occurred during the months of May, June and July.

Presented before the meeting of Region I, American Academy of Pediatrics, Washington, D. C., April, 1940.

From the Children's Hospital, Washington, D. C.

TABLE I

MONTH AND YEAR OF ADMISSION TO HOSPITAL

CASE NO.	DATE	CASE NO.	DATE
1	Sept., 1930	10	Aug., 1937
2	June, 1931	11 and 12	May, 1938
3	July, 1931	13	June, 1938
4	July, 1932	14	July, 1938
5	July, 1933	15	Aug., 1938
6	May, 1935	16	Apr., 1939
7	June, 1935	17	June, 1939
8 and 9	May, 1936	18	July, 1939

TABLE II

NUMBER OF CASES ADMITTED PER MONTH

MO.	NO. OF CASES
April	1
May	5
June	4
July	5
August	2
September	1

Age and Sex.—The ages of the patients ranged from 9 months to 10 years. There were 15 white children and 3 colored; 10 were females, and 8 were males.

TABLE III

AGE

AGE	NO. OF CASES	AGE	NO. OF CASES
9 mo.	1	6 yr.	1
1 yr.	1	7 yr.	2
2 yr.	1	8 yr.	1
3 yr.	2	9 yr.	2
4 yr.	2	10 yr.	1
5 yr.	4		

Residence.—Twelve of the cases were from nearby communities and rural areas in Maryland, and 3 were from nearby Virginia. Three resided in the District of Columbia but gave a history of exposure to ticks in nearby Maryland.

History of Exposure to Ticks.—In 10 of the children a tick was found on the body either preceding or early in the illness. In the remaining 8 cases exposure in areas in which ticks were abundant was reported. Of the 10 patients reporting tick bite, one found a tick on the body two days prior to onset of illness; 2 patients, three days preceding illness; 1 patient, seven days prior to onset; 2 patients, ten days preceding onset; and one child, twenty-one days prior to the onset of the disease. It is probable in the last 3 cases that other ticks may have been on the body at a later date and were not discovered by the family. In 3 cases a tick was found on the body after the onset of the disease. In one of these children there was a small nodule behind the left ear at the site of

the removal of a tick. In the other 17 cases there were no signs of local reaction to the tick bite and no regional lymphadenopathy.

Fever.—In one-half of the cases the fever was of the continuous type, averaging 103° F. in 7 cases, a little lower in one case, and slightly higher in another. The fever in the other 9 cases was remittent, the temperature ranging from 101° to 105° F. The duration of the fever varied from nine to twenty-six days, the average being sixteen days. In the patients who recovered, the temperature returned to normal by lysis. The pulse was in proportion to the temperature, ranging from 120 to 150 at the height of the fever, averaging 130 beats per minute.

Eruption.—The rash characteristic both in type and distribution was present in every case. It was macular in 12 cases, and maculopapular in 6. In 11 cases the rash became petechial or purpuric. It was distributed over the entire body in 14 cases. In 9 of these 14 cases the rash was more marked on the extremities and present to a less extent on the face and trunk. In 2 cases the rash was present on the extremities and face only and in 2 other cases was confined to the extremities only. In 6 patients it was present on the palms of the hands and soles of the feet. In 11 of the 18 cases the rash began on the extremities. The day of appearance of the rash was obtained in 16 cases. In 2 cases each the rash was stated to have appeared on the first and on the second day of illness; in 5 cases, on the third day; in 3 patients each, on the fourth and on the fifth day; and in one case, on the tenth day although it may have occurred a day or two earlier. Thus in 11 cases the rash appeared from the third to the fifth day of illness. In one case the rash was evanescent, fading and reappearing in intensity in a few hours.

TABLE IV

DAY OF APPEARANCE OF RASH

DAY	NO. OF CASES
1st	2
2nd	2
3rd	5
4th	3
5th	3
10th ?	1
Unknown	2

Physical Signs and Symptoms.—In addition to the fever and rash, the following signs and symptoms were found in this series of 18 cases, and the frequency of their occurrence has been noted. Next in frequency to the rash and fever, irritability was the most common symptom and was present 13 times. Constipation was present in 12 children; drowsiness and anorexia, in 11. Headache and vomiting occurred in 10 patients, mostly at the onset, but in a few children, during the course of the illness as well. Abdominal tenderness was present in 7 cases; abdominal pain, in 6 cases; and abdominal distention, in 5 cases. A palpable spleen was

present in 6 patients. In one case the spleen, which was not palpable on admission, rapidly enlarged until in about two or three days it was about 2 cm. below the costal margin. Pain in the extremities was complained of in 5 cases. Edema was present in 4 cases and occurred during the course of the disease. In 2 cases the edema was general, while in one case it involved the hands and feet, and in another, the feet and face. Hyperesthesia, conjunctivitis, and meningismus were present in 4 children. Stomatitis was also noted in 4 cases. In two of these, white spots were present on the buccal mucous membrane, and in one case there was a dirty gray exudate on the roof of the mouth. Dizziness was complained of in 3 instances. Delirium, a dusky tinge to the skin, and photophobia were noted in 2 patients. Cough was a symptom in 4 cases; in 2 of these there was definite evidence of bronchitis. Sweating occurred in two patients; chilliness, in one. These symptoms were noted during the course of the illness. Petechial spots on the soft palate were noted in one case. Deafness was present in one case. In one fatal case there were lethargy and coma for a period of twelve days prior to death. Repeated convulsions occurred during this period. Although there was a concurrent *Streptococcus hemolyticus* septicemia in this case, the lesions in the meninges and brain found post mortem were those of Rocky Mountain spotted fever. In the majority of the cases there were some signs of an upper respiratory infection, and otitis media was present in three cases.

TABLE V

INCIDENCE OF SIGNS AND SYMPTOMS IN ADDITION TO FEVER AND RASH

SYMPTOM	NO. OF CASES	SYMPTOM	NO. OF CASES
Irritability	13	Hyperesthesia	4
Constipation	12	Conjunctivitis	4
Drowsiness	11	Meningismus	4
Anorexia	11	Stomatitis	4
Headache	10	Dizziness	3
Vomiting	10	Delirium	2
Abdominal tenderness	7	Dusky tinge to skin	2
Abdominal pain	6	Photophobia	2
Palpable spleen	6	Coughing	4
Abdominal distention	5	Sweating	2
Pain in extremities	5	Chilliness	1
Edema, general	2	Petechial spots on soft palate	1
Edema, hands and feet	1		
Edema, feet and face	1	Deafness	1
		Convulsions	1

Results of the Weil-Felix Test.—The agglutination of Proteus OX-19 in the strength of dilution, as well as the day of disease, is given in Table VI. It will be seen that most of the positive agglutinations were obtained in the latter part of the second week and in the third week of the disease. A positive reaction may not occur until the period of convalescence, and in some cases does not occur at all.

TABLE VI

RESULTS OF THE WEIL-FELIX AGGLUTINATION OF PROTEUS OX-19

CASE	FIRST WEEK	SECOND WEEK	THIRD WEEK
1	Negative (5th day)	1:2500 heart's blood post mortem 9th day	
2	Not done		
3			1:5120 (19th day)
4	1:320 (6th day)		1:160 (20th day)
5		Complete 1:160 Partial 1:320 } 8th day	
6			Negative (15th day) Complete 1:800 (24th day) Partial 1:1600 (24th day) Post mortem 26th day 1:1280 complete 1:2560 partial
7		1:200 (12th day)	Complete 1:100 (20th day) Partial 1:200 (20th day)
8			1:320 (15th day)
9		1:40 (11th day)	
10	Not done		
11	Negative (3rd day)	Negative (13th day)	
12		1:1000 (14th day)	
13		1:40 (10th day)	
14	Negative (5th day)	1:2560 (14th day)	
15		Negative (8th day)	Negative (18th day)
16		1:1280 (11th day)	
17	Negative (7th day)	1:320 (13th day)	
18	Negative (4th day)	Negative (8th day) 1:80 (11th day) 1:640 (12th day)	

Blood.—The leucocyte count during the first week of the disease ranged from 4,300 to 29,700 per cubic millimeter, averaging 15,450 with 79 per cent polymorphonuclears, 44 per cent of which were segmented, 30 per cent staff form, and 5 per cent metamyelocytes. The lymphocytes averaged 20 per cent and the monocytes 1 per cent. The leucocyte count during the second week ranged from 5,800 to 27,000, averaging 14,220 with 75 per cent polymorphonuclears, 58 per cent of which were segmented, 15 per cent staff forms, and 1 per cent metamyelocytes. The lymphocytes averaged 24 per cent, and the monocytes 1 per cent. In both the first and second weeks of the disease the count may vary from a leukopenia to a marked leucocytosis although the average count showed a moderate leucocytosis. In one case, however, there was a leukopenia throughout the course of the illness. The differential count in this series showed more of a predominance of staff and young forms the first week than in the second week of the disease. Other series in adults stress the fact that there is a relative increase in the monocytes in Rocky Mountain spotted fever. This is not brought out in our series, in which the monocyte count is within normal limits.

Urine.—The urine was negative in eleven cases. Four children had febrile albuminuria in amounts averaging from 5 to 80 mg. per 100 c.c.

In two cases albumin and casts were found. In one fatal case the urine contained 100 mg. of albumin per 100 c.c. hyaline and granular casts, and red blood cells.

DIAGNOSIS

1. *Typhus Fever.*—Endemic typhus fever must be differentiated from Rocky Mountain spotted fever in some localities. In 1931 Rumreich, Dyer, and Badger[1] gave a clinical and epidemiological differentiation. They call attention to the following:

ROCKY MOUNTAIN SPOTTED FEVER	ENDEMIC TYPHUS FEVER
More prevalent in spring and early summer	Late summer and fall
Residence—rural	Residence—urban
Exposure to ticks	History of association with rats
Incubation—2 to 12 days (usually 7 days or less)	Incubation—6 to fourteen days
Pulse in proportion to fever	Pulse—slow
Rash first on wrists and ankles—2 to 5 days; palms and soles frequently involved	Rash first on chest and abdomen—5 to 7 days. Rash on palms and soles infrequent

2. *Typhoid Fever.*—Some cases of Rocky Mountain spotted fever, in which there are toxemia, continuous fever, and rash, are difficult to differentiate from typhoid fever. Particularly is this true if they are seen before the rash appears. While the rash in typhoid fever is usually hyperemic and limited, it may in some cases be quite extensive and petechial or purpuric. Specific agglutination tests and cultures are often required. In our 18 cases typhoid fever was considered in the diagnosis in 6 patients. Cultures and agglutination tests, however, were all negative.

3. *Appendicitis.*—In the first case of our series the abdominal signs and symptoms were those of acute appendicitis. In addition the leucocytosis was confirmatory, and the appendix was removed. The differential diagnosis from appendicitis, especially before the appearance of the rash, is at times difficult.

4. *Septicemia.*—Blood stream infection with streptococci and meningococci may produce confusing pictures. Blood cultures were taken in 6 cases to exclude blood stream infection. In one fatal case a blood culture from the heart's blood post mortem gave a growth of *Streptococcus hemolyticus.* This concurrent septicemia was not diagnosed during life.

In 6 of the cases in this series nervous and mental symptoms were conspicuous, and in 4 of these there was meningismus. These symptoms and signs, together with the rash, made it necessary to exclude meningococcus meningitis. Lumbar puncture was performed in all of these children. In 5 cases the cerebrospinal fluid was clear, colorless, under no increase in pressure, and normal both chemically and cytologically. In one fatal case, in which there was a concurrent *Streptococcus hemolyticus* septicemia, the fluid contained 11 cells (9 polymorphonuclears and 2

lymphocytes), no reduction of Benedict's solution, and an increase in globulin. No organisms were found on smear or culture. In this case the lesions found post mortem in the meninges and brain were those of Rocky Mountain spotted fever.

MORTALITY

There were 3 deaths in the series (Cases 1, 6, and 10), or a mortality of 16.6 per cent. The first death occurred on the ninth day of the disease. This child was the first patient with Rocky Mountain spotted fever admitted to the hospital. The second fatal case had an accompanying *Streptococcus hemolyticus* septicemia, and death occurred on the twenty-sixth day of the disease. The third child was admitted on the fourteenth day of the disease and died thirty hours later of a virulent type of infection. Post mortem examination was made in each case, and the diagnosis was confirmed. The other 15 patients had an uneventful recovery.

TREATMENT

The treatment of these children was about the same although they were on the service of different members of the staff. It was largely symptomatic and supportive. Good nursing care was found to be essential. Nutrition was maintained by an adequate liquid and soft diet. In a few children there was marked anorexia, and for a time they were fed by gavage. Fluids by mouth were forced, and occasional clysis was given. An ice cap to the head and sponge baths were used to control the temperature. Blood transfusions were given in three cases. In one fatal case three transfusions were given and in another fatal case five, four of which were from an immune donor. One child received one transfusion, and another was given immune blood intramuscularly. Both of these children recovered. In recent years many physicians of wide experience with spotted fever have advised against transfusions and intravenous fluids. They have observed that patients receiving this type of treatment do not do so well as those who do not receive this therapy. This advice has been followed at the Children's Hospital, and for the past several years intravenous therapy has not been practiced. We wish to emphasize that there is more danger from overtreatment of these patients than from undertreatment.

REFERENCE

1. Rumreich, Dyer, and Badger: Pub. Health Rep. V-46: 479, 1931.

PEPTIC ULCER IN CHILDREN

Report of Ten Cases

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NO CLINICIAN likes to be embarrassed at the autopsy table; yet that is what is likely to happen in the case of peptic ulcer in children unless he is closely on his guard. The symptoms of peptic ulcer in children are not typical, as they are in adults. The characteristic hunger pain, relieved by food, does not occur in children until they approach the age of adolescence. Nor can the epigastric tenderness be localized in children as in adults. We must usually depend upon the history gained from the parents and, especially, upon roentgenographic examinations. We must be conscious of the fact that peptic ulcer does occasionally occur in children, or we will not recognize the cases until some alarming symptom, such as perforation or hemorrhage, forcibly calls this diagnosis to our attention; then, perhaps, the autopsy will prove the diagnosis, whereas the roentgenogram should have proved it earlier. I shall cite two cases diagnosed at post-mortem examination.

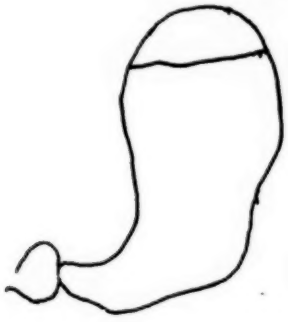

Fig. 1.—Normal.

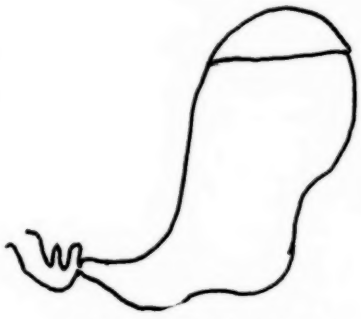

Fig. 2.—Duodenal ulcer.

It is very difficult to obtain x-ray pictures which show the typical defects of peptic ulcer in children. The only way one can be sure of demonstrating these defects on a film is to take about forty serial plates one minute apart, and this is impractical. The diagnosis is made mainly by the fluoroscope and supported by x-ray film. To show these defects, I have prepared a series of diagrams: Fig. 1, the normal stom-

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From the Department of Pediatrics, Georgetown University.

ach and duodenum; Fig. 2, the deformity of the duodenal cap in duodenal ulcer; and Fig. 3, gastric ulcer on the lesser curvature with incisura.

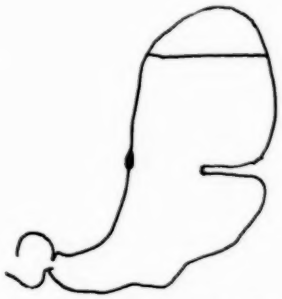

Fig. 3.—Ulcer on lesser curvature with incisura.

To emphasize further the subject of peptic ulcer in children, I have made a survey of the cases occurring at Children's Hospital from 1932 to 1939, inclusive. Out of 21,231 admissions there were 8 cases of peptic ulcer, 6 of which were duodenal and 2 of which were gastric. We have positive fluoroscopic and x-ray evidence on all except 3 cases. Two of these were diagnosed at the autopsy table, and one was diagnosed clinically. In addition to these, 2 cases seen in private practice are included.

CASE REPORTS

Case 1.—M. S., white male, aged 7 years, was admitted to Children's Hospital on Nov. 25, 1932, with abdominal pain and several tarry stools per day prior to admission. He vomited a large clot of blood following a transfusion.

Fluoroscopic examination revealed a constant deformity of the duodenal cap, with 10 per cent six-hour residue of barium in the stomach. Re-examination three months later showed no six-hour residue but a persistence of the defect in the duodenum. A follow-up x-ray study five months later showed the stomach and duodenal cap to be normal. This patient was treated with a modified Sippy diet, then a smooth bland diet followed by a nonroughage diet containing puréed vegetables, etc.

Case 2.—L. L., white female, aged 6 years, was admitted on Oct. 21, 1935, with a temperature of 104° F., and the complaint of drowsiness and stiffness of the neck. Physical examination showed signs of pneumonia in the right lower lobe. The abdomen was negative. Any movement of the child was very painful. Spinal fluid examination was negative. X-ray showed inflammatory process of the right lower lobe.

The child died on Oct. 25, 1935. Autopsy revealed pneumonia and empyema of the lower lobe of the right lung and an old gastric ulcer on the greater curvature. The stomach contained about 500 c.c. of clotted blood, and the whole gastrointestinal tract was filled with reddish black tarry fluid from the stomach to the rectum.

Apparently this child had an old gastric ulcer which had not been diagnosed. She came to Children's Hospital with pneumonia and died of a massive hemorrhage of the ulcer.

CASE 3.—R. M., white female, aged 9 years, was seen in the outpatient department complaining of belching after meals for the past three years. No pain, burning, vomiting, or nausea accompanied this symptom. Fluoroscopic examination at that time showed a constant defect of the duodenum due to an ulcer. The child was placed on a Sippy diet and was given antacid powders. A recheck by fluoroscope on May 12, 1938, showed that the duodenal cap filled normally, and the child had no further complaints.

CASE 4.—P. H., white female, aged 13 years, was admitted to Children's Hospital on Feb. 12, 1939, with a chief complaint of weakness for a period of one week. For the past six months the patient had suffered from vague abdominal pain occurring with the onset of menstruation. This abdominal distress was temporarily relieved by taking food. Her appetite became poor with the onset of her trouble. Two days before admission, while at the movies, she suffered a sudden attack of nausea and vomited blood. The next day she vomited, but no blood was seen. The following day, the day of admission, she vomited coffee-ground material. Her stools had been tarry for several days prior to admission.

Her hemoglobin was 30 per cent, and the red cells numbered 1,790,000. She received five blood transfusions and was discharged on Feb. 24, 1939, with a hemoglobin level of 71 per cent and 3,770,000 red blood cells.

No x-ray studies were done at this time on account of her severe hemorrhage, but the clinical diagnosis was hemorrhage from a peptic ulcer.

I cite this case, even though we have only a clinical diagnosis, because her symptoms were typical of duodenal ulcer in the adult, i.e., hunger pain relieved by food. Two months later, x-ray studies revealed a normal stomach and duodenal cap. As was stated before, in a child of this age the symptoms may be typical as in the adult.

CASE 5.—W. G., white female, aged 10 years, was admitted to Children's Hospital on March 13, 1936, with a complaint of vague abdominal pain associated with nausea throughout childhood. The pain was more acute for a week prior to admission. The child was described as having a neurotic temperament. Fluoroscopic examination of the stomach showed a definite niche and a deformity in the prepyloric region of the stomach on the lesser curvature, due to an ulcer. The appendix was visualized and was definitely tender and rigid. It was removed and found to be pathologic. The child was placed on a modified Sippy diet. Fluoroscopic examination on July 27, 1936, showed no demonstrable ulcer in either the stomach or duodenum, and the child had no further pain or nausea.

CASE 6.—M. C., white female, aged 5 years, was admitted to Children's Hospital on Jan. 30, 1939, as a problem in feeding, with the complaint of anorexia. Fluoroscopic examination revealed a constant fleck, and the duodenal cap could not be filled. After administration of belladonna, the fleck remained, and the duodenal cap showed a constant deformity. The child was discharged from the hospital on Feb. 4, 1939, and, because of poor cooperation of the parents, she has not been rechecked by the fluoroscope.

CASE 7.—W. R., white male, Mongolian idiot, aged 3 weeks, was admitted to Children's Hospital on June 4, 1938, because of regurgitation and vomiting since birth. The vomitus was bile stained. The stools were scant but fecal in character. No hemorrhage was noted.

The clinical diagnosis was congenital defect of the bowel in the region of the duodenum. The patient died on July 7, 1938, and the autopsy revealed a congenital incomplete obstruction at the duodenojejunal junction and an ulcer of the lower duodenum 0.2 cm. in diameter. This represents a peptic ulcer of the newborn due to congenital anomalies about the duodenum.

CASE 8.—J. B., a white boy, aged 4½ years, was admitted to Children's Hospital on June 9, 1939. He had the following history. For the past five or six months he had been having occasional black, sticky, tarry stools. Just prior to admission he had from four to eight per day with a seeming loss of sphincter control. There had been no nausea or vomiting. From time to time he had complained of some abdominal discomfort but not very often. This was not related to meals or bowel movements. Mother, father, and three older siblings were living and well. He had had pertussis at 2 years of age with complete recovery and was said to have had rickets between the ages of 9 and 15 months.

Physical examination was essentially negative except for slight cervical adenitis and a low-grade tonsillar infection. There were no abdominal masses and no tender spots. His speech was rather mumbling and difficult to understand.

Gastrointestinal series at the time of admission showed a deformed duodenal cap which would not fill. Two weeks prior to admission he had been treated in southern Maryland by a local doctor for a week on a strict milk diet (every two hours). The mother stated that his stools had cleared up considerably. He had no more tarry stools after admission to the hospital, and we kept him on a smooth bland diet.

X-ray examination on June 19, 1939, showed the duodenal cap to be still deformed. He was discharged on June 27, 1939, nineteen days after admission, on a diet free of roughage. He had gained 5 pounds in weight.

Re-examination by x-ray two months later showed the ulcer to be entirely healed, and the duodenal cap filled normally.

CASE 9.—D. M., white female, aged 4½ years, was seen on March 26, 1940, complaining of abdominal pain at irregular intervals accompanied by pallor during the attacks. She had also been having several black tarry stools per day with apparent loss of sphincter control during the previous two weeks. Physical examination was entirely negative.

Gastrointestinal x-ray studies were carried out on March 27. The duodenal cap could not be visualized. On April 8 she was re-examined after the administration of belladonna. The duodenal cap failed to fill at any period of the examination. A diagnosis of duodenal ulcer was made at this time, and appropriate treatment begun.

On June 3, about two months after the original gastrointestinal series, another fluoroscopic and x-ray study was made. The duodenal cap was visualized, and, although somewhat deformed, it emptied completely.

She has been symptom free since the first week of the treatment and now seems very well. She is still being given a diet free of roughage.

CASE 10.—M. H., a white female, aged 9 years, was first seen by me on Feb. 22, 1940, complaining of frequent upper abdominal pains with belching for the past five or six years. This pain was characterized by food relief at times. Bowels were habitually constipated, but stools never tarry. Roughage and excessive sweets in the diet seemed to bring on the attacks of abdominal pain. She was well nourished, and physical examination was essentially negative except for tenderness over the epigastrium and a moderate secondary anemia.

X-ray studies of the gastrointestinal tract revealed 25 per cent gastric retention of barium at the end of five hours. The duodenal bulb was visualized and appeared to fill normally. The appendix was moderately large, irregularly filled, freely moveable, and not tender. The x-ray diagnosis was partial obstruction of the stomach at the pylorus and a large irregularly filled appendix.

The patient was put to bed for a week and given belladonna before meals and a modified Sippy diet. Then she was given a very smooth bland diet and allowed to be out of bed. She was symptom free until April 21, when she had an attack

of acute abdominal pain followed by vomiting of partially digested blood. This attack followed attendance at a children's party.

She was re-examined by x-ray on April 23. Findings were essentially the same in spite of intensive treatment. The roentgen diagnosis at this time was peptic ulcer in the pyloric ring or on the duodenal side.

She is still being treated medically, but it appears likely that her condition may require surgery if the pyloric obstruction increases or cannot be relieved in the due course of time.

CONCLUSION

We have cited eight cases of peptic ulcer occurring in Children's Hospital from 1932 to 1939, inclusive, out of 21,231 admissions, and two cases seen in private practice.

We would advocate a freer use of the x-ray in children with such complaints as anorexia, retarded growth, vague abdominal distress, and constipation. By so doing, the diagnosis may be made before some alarming symptom, such as hemorrhage or perforation, forcibly calls this diagnosis to our minds, thereby perhaps saving the life of a child.

I wish to gratefully acknowledge the assistance given me by my associate, Dr. Harold M. Hobart, in collecting these case histories and in abstracting them. I wish also to thank Dr. John H. McLeod, Dr. H. Lynn Colvin, Dr. Robert A. Bier, and Dr. Herman Eisenberg upon whose services some of these cases occurred.

MASSIVE UNILATERAL PULMONARY FIBROSIS DUE TO OBSTRUCTIVE TRACHEOBRONCHIAL TUBERCULOSIS

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THE etiology of extensive unilateral pulmonary fibrosis has never been explained to the satisfaction of all investigators. During the past forty years controversial opinions have appeared relative to the evolution of this disorder. Writers have searched for evidence to prove that fibrosis always followed an antecedent infection. Since this was not forthcoming, it has been maintained that in rare cases the stroma of the lung might increase progressively in amount without the stimulus of a known acute process. Abraham Jacobi[1] was one of the earliest proponents of this possibility. The same view was shared by Norris and Landis,[2] in whose textbook may be found the statement, "Pure fibrosis of the lung, although rare, does, however, exist." Accurate descriptions of the onset of the disease are not available because in most instances the picture is fully developed at the time of the first examination. Pathologic reports have serious limitations since the illness is of such long duration that the initial lesion may be obscured completely at autopsy.

It is generally admitted that tuberculosis is the disease most commonly associated with extensive unilateral fibrosis. Syphilis, abscess, infarct, and mycotic infections are among the rarer causes. Extrapulmonary growths and effusions by reason of pressure exerted on the pulmonary tissue may lead to fibrotic changes. Only bilateral lesions follow the inhalation of dust. Since all of the latter causes may be proved easily at autopsy, it has been customary to attribute the majority of the remaining cases to the tubercle bacillus. It was formerly believed that the conditions responsible for the production of this disorder existed when the balance between the virulence of the organism and the resistance of the host was so nearly even that the fibrosing process kept pace with the ulcerative lesions.

With the advent of bronchoscopy the above explanation is no longer tenable. Massive fibrosis is neither a disease sui generis nor the end result of a pulmonary inflammatory reaction. It follows purely physical and mechanical alterations in which bronchial obstruction produces massive atelectasis which subsequently becomes fibrotic. Hennell[3] has suggested that the correct point of view for purposes of classification is to apply to cases of obstructive tracheobronchial tuberculosis the types of bronchial obstruction defined by Chevalier Jackson.

From the Children's Hospital.

1. By-Pass-Valve Obstruction: This type is a partial obstruction which permits both ingress and egress of air past the obstruction, and which does not cause either collapse or emphysema of the tributary lung. These cases are common in children under two years of age and are characterized clinically by expiratory stridor and a bitonal cough. The similarity of the physical findings to those of asthma is well known.

2. Check-Valve Obstruction: This type allows the air to pass in during inspiration, when the bronchial diameter is increased, but prevents the egress of air from the alveoli during expiration. Such cases show enlargement of the chest on the affected side, widening of the intercostal spaces, limitation of respiratory movement, displacement of the heart to the opposite side, hyperresonance, diminution of breath sounds, and immobility of the diaphragm. X-ray confirms the diagnosis of emphysema. Illustrations are contained in the case reports by Faust[4] and by Spivek.[5]

3. Stop-Valve Obstruction: In this type the air cannot get in during inspiration or out during expiration. Following this obstruction, the alveolar air is absorbed by the pulmonary circulation, and atelectasis results. It is this type that is believed to be responsible for massive unilateral fibrosis.

The clinical picture presented by the latter group has many variations. A few symptoms, however, recur with sufficient frequency to permit a general description. The onset is usually insidious, and only rarely is a case observed from its incipiency. A chronic cough is the predominant symptom. Dyspnea and palpitation are often present but are not so severe as to prevent a fair degree of health. The physician is surprised to find signs of extensive involvement of one lung with displacement of the heart and mediastinum toward the affected side. The picture is that of massive atelectasis (collapse). X-ray shows a uniformly dense shadow completely obscuring the lung with the occasional exception of bronchiectatic cavities. Tubercle bacilli are rarely found in the sputum, and attacks of toxemia do not occur. It is difficult to prove a tuberculous etiology.

This picture can be produced only when complete bronchial obstruction follows a primary tuberculous infection. The obstruction is the result of external compression by enlarged mediastinal glands. The initial pulmonary lesion heals completely. This explains the absence of tubercle bacilli in the sputa, the benign clinical course, and the difficulties that arise in the search for an etiologic agent.

In contrast to this benign course, a different clinical picture occurs when bronchial obstruction develops during active pulmonary tuberculosis. In such an instance, complete healing may not ensue, and tubercle bacilli are often found in the sputa. The obstruction in this group is more often due to lesions of the bronchial wall from ulcerating glands or to direct contact with bacillary sputa. Pierson and Samson[6] have at-

tempted a classification of the bronchial lesion based on bronchoscopic findings. They describe a mucosal ulceration with obstructing granulation tissue; a submucosal lesion covered with edematous, granular, and bleeding mucosa; and a fibrostenotic lesion that follows the healing of the first two types. Secondary infection with poor drainage because of the stenotic bronchus results in severe toxicity. Bronchiectasis frequently occurs and likewise multiple abscesses.

The development of bronchiectasis in this latter group is undoubtedly favored by actual infection and destruction of the bronchial wall either by the tubercle bacilli or by pyogenic organisms. Its occurrence in the benign types, in which atelectasis is present without infection, has been the subject of considerable speculation. The relationship between bronchiectasis and atelectasis has been discussed recently by Andrus.[7] In cases of atelectasis involving part of a lung, the lost space is occupied by adjoining structures with overexpansion of the pulmonary tissue. Since negative intrapleural pressure is due to the elastic recoil of the lung, it is increased when the elastic tension increases. The compensatory expansion of the adjacent lung represents a state of elastic hypertension. This produces an increase in negative pressure as proved by measurements in intrapleural pressure in cases of atelectasis. Centrally it produces a corresponding increase in dilating stress upon the bronchi of the affected region. The bronchi in this area will suffer to a greater degree if the walls have been weakened by infection. When atelectasis extends throughout an entire lung, the development of bronchiectasis may be due to the contraction of fibrous tissue. In order for this to occur, according to Andrus, there must exist continuity of fibrous tissue across the complete width of the lung and rigidity of anchorage at opposite faces. This must represent a very rare possibility.

The exact explanation for the conversion of atelectatic tissue into fibrous tissue is likewise not clearly understood. The element of time is important, for, if the obstruction is relieved early, the lung will reexpand. This is true in most instances of post-diphtheritic and postoperative collapse. It is known that the lung may be kept collapsed by means of artificial pneumothorax for several years and yet suffer no damage. In such instances, the bronchi may be distorted but practically never narrowed or obliterated. When collapse is dependent on obstruction of a bronchus, fibrosis may occur early. Consequently one may infer that the absence of air is the deciding factor. The changes observed at autopsy closely simulate those which follow inflammation. Findlay[8] states that the end results in atelectasis and unresolved pneumonia are indistinguishable. The possibility of a secondary low grade, nonspecific infection in the atelectatic area must be considered. It is difficult to estimate the importance of the various physical changes that take place with shrinkage of the lung. There is a decrease in distensibility, reduction in air exchange, decrease in blood flow, passive hyperemia, anox-

emia, lymphostasis, and tortuosity, strangulation, and obliteration of the vessels. The subject is of great importance for those interested in attempts to heal tuberculosis by the production of artificial bronchial obstruction from scarification of the mucosa with chemical agents (Adams and Vorwald[9]).

Cases of unilateral massive fibrosis are frequently described in the literature pertaining to adult tuberculosis. Many instances are recorded by Hennell,[10] Stivelman,[11] Habliston,[12] Packard,[13] and others. In children the condition is a great rarity. Although slight bronchial obstruction occurs in many cases of fresh primary tuberculosis and areas of atelectasis of varying degrees are likewise not unusual, the complete fibrosis of one lung is not often encountered. This is surprising when one considers that enlargment of the mediastinal glands is by definition an accompaniment of every case of childhood tuberculosis. In none of the cases studied by McPhedran,[14] including those in which the nodes were enormously enlarged, were there any obstructive symptoms. In a footnote he refers to a child who died of tuberculous meningitis and at autopsy showed a huge mass of glands at the left of the trachea, displacing it to the right and narrowing the lumen of the left main bronchus, without producing atelectasis.

Stoloff[15] has reported a case of massive atelectasis of the left lung in a 2-year-old child infected with tuberculosis. The basic cause of the atelectasis is attributed to enlargement of the regional lymph nodes caused by a fresh primary tuberculous complex, this enlargement being sufficient to occlude the already inflamed bronchus. After one week a restitution of the collapsed lung to normal aeration occurred. The onset of the illness was characterized by restlessness, irritability, and fever. Dyspnea was never severe, and only a slight cough was present. In the absence of a careful physical examination similar cases may be overlooked.

Lerche[16] has described a case of massive collapse due to bronchial obstruction from enlargement of a congenitally malformed heart. The child was a 3-month-old twin whose symptoms began at six weeks of age. The left main bronchus was compressed by the heart below and by lymph nodes above. The tuberculin test was negative. No mention is made of microscopic examination of the nodes or lung. It is interesting that an x-ray diagnosis of malignant growth of the affected lung was made in this instance as well as in one of our cases. The two conditions may often be differentiated by measuring the intrapleural pressure.

Instances of atelectasis of parts of the lung have been observed by Wallgren,[17] Wessler and Jaches,[18] Wilson,[19] and others. Narrowing of the right lower bronchus due to tuberculous granulation tissue was proved by bronchoscopic examination in Wilson's case. Wallgren emphasizes the occasional intense desquamation of epithelium which takes place in the compressed bronchus as an important contributing factor. When this is associated with specific tuberculous changes in a small

bronchial branch, he believes that atelectasis may occur without the necessity of any great degree of external pressure.

Armand-Delille and Inbona[20] describe a 14-year-old boy with symptoms of one year's duration. The onset was characterized by fatigue and loss of appetite. The tuberculin test at this time was strongly positive. His mother died of pulmonary tuberculosis one year prior to the onset of the patient's illness. Six months after admission to a preventorium he developed fever, slight dyspnea, and pains over the left thorax. Five months later he had his first hemoptysis. Examination at this time showed extensive consolidation of the entire left side. He was not dyspneic nor critically ill and coughed only occasionally. Stomach washings failed to show tubercle bacilli on culture or guinea pig inoculation. X-ray showed a marked opacity of the left side with no mention made of the position of the heart. Two more episodes of hemoptyses occurred. Clubbing of the fingers developed during observation. No lipiodol entered the bronchi of the upper lobe of the affected lung. Bronchoscopy revealed a definite stenosis at this area with hyperemia and bleeding at the orifice. Bronchoscopic drainage of large amounts of purulent secretion resulted in marked improvement in general health.

An analysis of this report suggests classification in the first group in which collapse and fibrosis have occurred with healing of the specific lesion. All the symptoms are referable to the presence of bronchiectasis and not to active tuberculosis.

Lightwood and Wilson[21] have reported the best example of an entire fibroid lung associated with bronchial obstruction that we have been able to find in the pediatric literature. Their case occurred in a 5-year-old boy who had pneumonia on two previous occasions. Examination showed signs of massive collapse of the left lung. The tuberculin test was strongly positive; the sedimentation rate was not increased; there was no leucocytosis. Thoracentesis showed an increase in negative pressure. Bronchoscopy revealed a narrowing of the left main bronchus. Lipiodol instillation confirmed their diagnosis of bronchiectasis. Successful pneumonectomy was performed. Suggestive but not diagnostic evidence of tuberculosis was obtained from the histologic sections.

Two cases have recently been observed at the Children's Hospital in Los Angeles. Prior to exitus, the patients were removed to other institutions, and unfortunately complete autopsy studies are not available.

CASE 1.—A white girl, aged 14 months, was admitted to the Children's Hospital with the complaint of failure to gain weight. Her progress had been uneventful until 7 months of age. At this time she contracted a respiratory infection, diagnosed as pneumonia. Improvement occurred after two weeks' illness, but not a complete recovery. Poor appetite, a mild cough, and failure to gain weight were the only symptoms described. The weight on admission was 9½ pounds, an increase of only 4 pounds above the birth weight.

Examination showed an undernourished child, resting comfortably and not acutely ill. The percussion note over the left lung was dull; the breath sounds were distant and tubular; no râles were audible. There were no extrapulmonary findings. The

x-ray showed a completely homogenous shadow over the entire left chest. The following diagnoses were considered: a benign or epituberculous consolidation; a caseous tuberculous pneumonia; an unresolved pneumonia (nontuberculous).

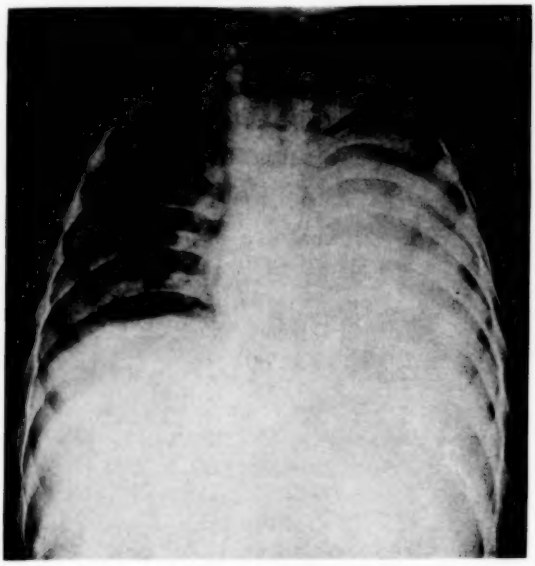

Fig. 1.—Case 1. Massive collapse of the left lung about seven months after the onset of symptoms.

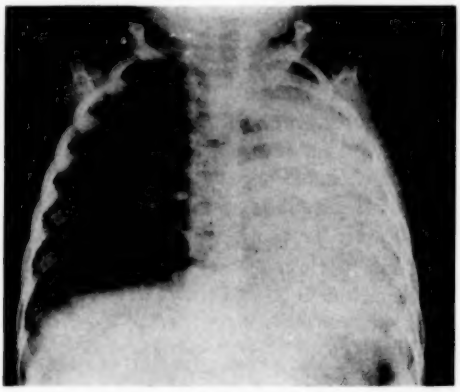

Fig. 2.—Case 1. Thirteen months after onset showing greater displacement of the heart toward the affected side.

The hemoglobin was 65 per cent; red cell count 3,990,000; white cell count 14,550 with 47 per cent polymorphonuclear cells. The intradermal tuberculin test, 0.1 mg., was strongly positive. Tubercle bacilli could not be found in the material obtained from gastric washings. Sputum examinations were negative for tubercle bacilli. Lung puncture on three occasions failed to show tubercle bacilli in the aspirated material on direct smear or guinea pig inoculations.

During the next five months she gained 5 pounds and her condition slowly improved. She appeared to benefit from two blood transfusions. The temperature remained consistently normal.

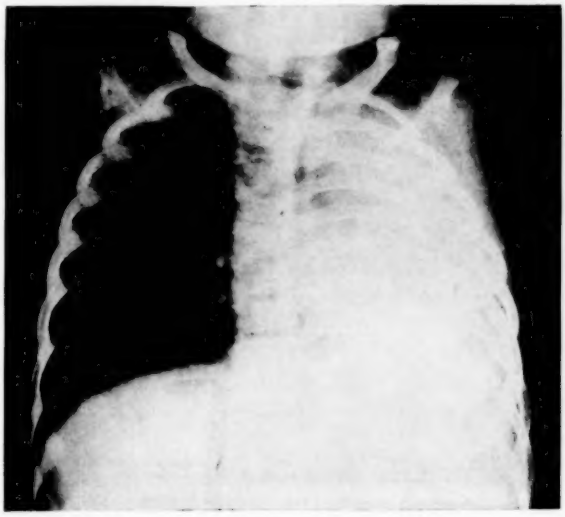

Fig. 3.—Case 1. Twenty-five months after onset. The intercostal spaces on the affected side have become narrower.

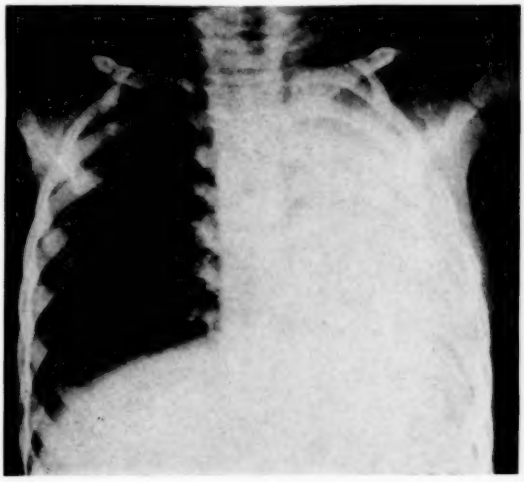

Fig. 4.—Case 1. Thirty-seven months after onset. No change in physical signs.

Subsequent x-rays showed the heart displaced towards the left side. The pictures were consistent with a massive atelectasis. The possibility of a foreign body was considered, and a bronchoscopic examination was made. This showed compression of the trachea and left bronchus by mediastinal glands. The obstruction did not appear sufficient to cause collapse, and nothing abnormal was noted in the lumen.

She convalesced satisfactorily from an attack of measles. At 28 months of age, her weight was 20 pounds. The physical signs and x-ray findings remained unchanged.

At 5 years of age, she was admitted to the Los Angeles County Hospital. The development of bronchiectasis in the affected lung was the only change that had occurred. Two months later pneumonectomy was performed, but death occurred a few minutes after the lung was removed.

The pathologic report of the left lung showed a fibrotic mass measuring 7 by 5 by 2 cm. It was covered by dense fibrous adhesions at all surfaces. The interlobar fissure was obliterated. The lung parenchyma was entirely replaced by pearly white fibrous tissue. The bronchial tree and its saccular dilatations were filled with pus. The pulmonary artery appeared normal. No definite tuberculous lesion was found in the lung. No record could be found of the examination of the glands.

The mechanism producing the collapse in this case was probably similar to the one reported by Stoloff. Enlargement of the regional lymph nodes caused by a fresh primary tuberculous complex compressing the left bronchus produced a massive collapse. One may theorize that a longer time interval occurred than in his case, and hence the development of fibrosis. With subsequent diminution in the size of the glands, the bronchus again became patent. In the interim the primary lesion healed.

CASE 2.—A white male, aged 20 months, was admitted to the Children's Hospital with the complaints of cough, dyspnea, and febrile episodes of one year's duration. The illness began with a respiratory infection and a severe cough. A few months later an exacerbation, diagnosed as bronchopneumonia, occurred. An x-ray at this time showed a density involving the upper two-thirds of the left chest. This was interpreted as a mediastinal tumor, probably lymphosarcoma. Twenty-two x-ray treatments were administered over a four-month period. An initial improvement was followed by increasing weakness, loss of appetite, and irritability.

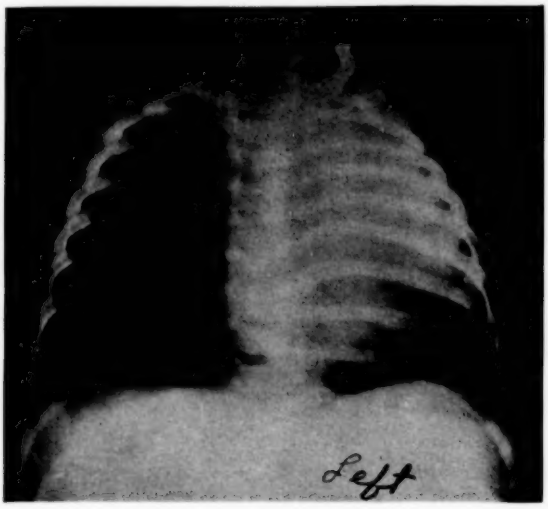

FIG. 5.—Case 2. Approximately two months after the onset of symptoms. Massive collapse of the left lung.

Examination showed a pale, undernourished child with a slight degree of dyspnea. The left lung was completely consolidated with displacement of the heart to the

affected side. In view of the long history and our experience in Case 1, a diagnosis was made of massive collapse with resulting fibrosis due to complete obstruction of the left main bronchus by tuberculous glands.

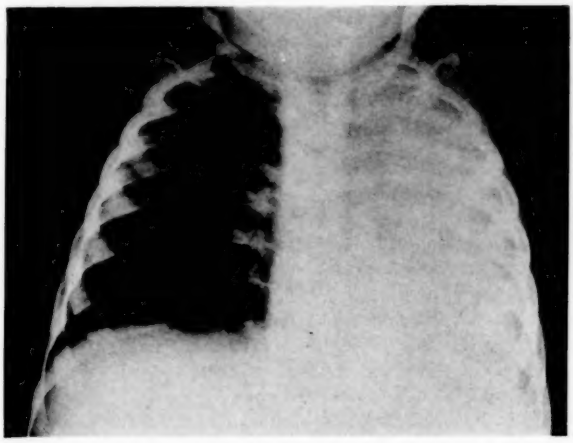

Fig. 6.—Case 2. Fourteen months after the onset of symptoms. Heart displaced to the left.

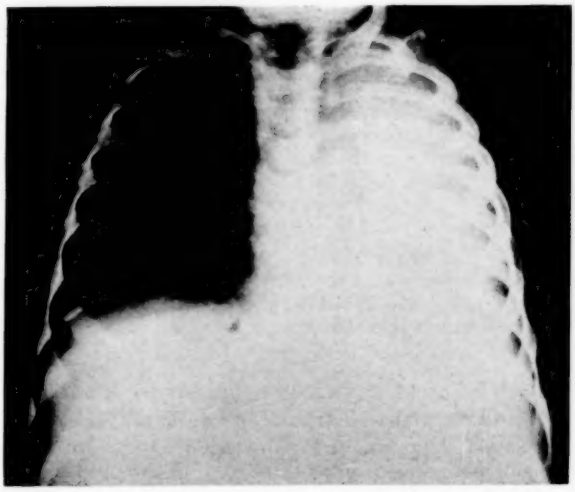

Fig. 7.—Case 2. Fifteen months after onset. No air has entered the left lung after removal of tuberculous granulation tissue from main bronchus. Narrow ring of calcification at periphery of apical lesion.

The intradermal tuberculin test, 0.1 mg., was strongly positive. The stomach washings failed to reveal tubercle bacilli. The hemoglobin was 45 per cent; red cell count 4,160,000; white cell count 19,850 with 65 per cent polymorphonuclear cells. The Wassermann and Kahn reactions were negative. The temperature remained slightly above normal with an occasional rise to 103 or 104° F.

Bronchoscopic examination showed a complete obstruction of the left main bronchus due to ragged granulation tissue. Biopsy of this tissue was characteristic of chronic inflammatory changes with a few typical tubercles. Removal of the obstruction failed to permit the entry of air to the lung as determined by physical signs. Lipiodol injection was unsuccessful as the oil entered the mediastinum. Death occurred suddenly nine days after bronchoscopy.

Autopsy showed extreme atelectasis with fibrosis and bronchiectasis due to compression of the left main bronchus. The tracheobronchial lymph glands showed extensive caseation. A definite stenosis of the left bronchus from external pressure was demonstrable. A large area of caseous necrosis was present in the left upper lobe. It was surrounded by a profound degree of fibrous tissue with occasional deposits of calcium. The pleura over this area was greatly thickened. The lung tissue elsewhere showed extensive fibrosis with only a few remaining alveoli. The stroma of the connective tissue was infiltrated with many round cells, occasional polymorphonuclear cells, and fresh tubercles.

A marked degree of bronchiectasis was present in the entire bronchial system. The bronchial walls were thickened with granulation tissue containing occasional tubercles and giant cells. A few areas of squamous-cell metaplasia had developed. There were many areas of intense inflammation covered with fresh purulent secretions in the larger bronchi. At the point where the obstructing granulation tissue had been removed, the bronchial wall was injured. This explained the lipiodol in the mediastinum and the presence of caseous necrotic tissue from the enlarged gland in the bronchial lumen.

There was also a perforation between the bronchus and an adherent portion of the esophagus. Tuberculous ulcers lined the wall of the entire small intestine and were associated with massive caseous tuberculous mesenteric adenitis.

This patient may be classified with the second group of cases in which bronchial obstruction occurred in an individual with active pulmonary tuberculosis. This explains the presence of signs of tuberculous toxemia during the entire illness. If one interprets the area of caseous necrosis in the upper lobe as the primary lesion, it is interesting to speculate on the absence of cavitation. Cavitation in such an area ordinarily occurs within four to six months after the appearance of a homogeneous shadow in the x-ray. Its absence in this case was in all likelihood due to the collapse produced by the bronchial obstruction which favors healing. The influence of the x-ray treatment is doubtful.

Since the right lung was unaffected, it is conceivable that a cure may have followed pneumonectomy. The operation was refused by the consulting thoracic surgeon because of the great risk of a subsequent miliary tuberculosis or death from meningitis.

The treatment of massive unilateral pulmonary fibrosis by collapse therapy is indicated in the absence of tracheobronchial ulceration. It relieves the cough, dyspnea, and palpitation and theoretically should help prevent the development of bronchiectasis. Should tracheobronchial ulceration exist, collapse therapy may add to the difficulty in raising sputum. If bronchiectasis is present and of such severity as to constantly undermine the patient's health, pneumonectomy must be performed. According to Samson,[22] in select cases symptomatic improvement has followed the bronchoscopic aspiration of retained secretions, chemical shrinkage of edematous mucosa, or the cautious dilatation of circumscribed bronchial stenoses.

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DIPHTHERIA TREATED UNSUCCESSFULLY WITH SULFONAMIDE COMPOUNDS

Report of Two Fatal Cases

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FAULKNER[1] and Bowman[2] have recently reported two cases of uncomplicated diphtheria in which sulfanilamide rendered the use of antitoxin unnecessary. They suggested independently the possible favorable action of sulfanilamide in infections due to the Klebs-Löffler bacillus. We wish, therefore, to record two fatal cases of proved diphtheria treated with azosulfamide and sulfanilamide, respectively, under apparently mistaken diagnoses of pseudomembranous hemolytic streptococcic sore throats.

Case 1.—J. O., female, aged 9 years, became ill with a sore throat and fever on May 17, 1940. The family physician took a throat culture and prescribed azosulfamide, 7.5 grains every three hours day and night. The culture was reported negative for Klebs-Löffler bacilli. Treatment with azosulfamide was therefore continued. The case was then taken over by another physician in the absence of the family physician. He saw the child May 19 and May 20 and continued the azosulfamide even though the child's condition was becoming progressively worse. She was seen in consultation by one of us (S. M. A.) on May 21. The findings at that time were those of a desperately ill, but conscious and cooperative girl of 9. Her temperature was 103° F. axillary, and her pulse, 130. Essentially, she presented the typical appearance of an untreated case of faucial and nasal diphtheria, with the characteristic bullneck type of cervical swelling and a profuse, glycerine-like nasal discharge. The soft palate and tonsillar areas were covered with an extensive, thick, brownish-gray false membrane. The uvula was necrotic. Examination of the posterior pharynx was unsatisfactory. Nose and throat cultures taken at this time were later reported positive for Klebs-Löffler bacilli. Immediate hospitalization was ordered, but the patient died before this could be carried out.

Case 2.—R. M., male, aged 16 years, was brought to the Cook County Contagious Hospital on July 17, 1940, from a hospital sixty miles away. The following history was obtained. The youth had been staying at a boys' camp where, on July 11, he became sick with fever and a sore throat for which no specific medication was given. When his condition did not improve, sulfanilamide in full dosage was ordered and given during the third and fourth days of his illness. Because he was getting worse, he was taken on July 15 to a near-by hospital, where 60,000 units of diphtheria antitoxin and intravenous glucose were administered. At his mother's insistence, he was moved to Chicago. Upon arrival he was unconscious and moribund. His temperature was 104° F., and his pulse, 140. The throat was covered with dirty-brown, bleeding false membrane from which smears and cultures were positive for Klebs-Löffler bacilli. Despite a blood transfusion and administration of intravenous glucose and ascorbic acid, he died eighteen hours after admission.

From the Department of Pediatrics, University of Illinois College of Medicine, and the Cook County Contagious Hospital.

SUMMARY AND CONCLUSIONS

Two fatal cases of diphtheria treated inadvertently with sulfonamide compounds to the exclusion of early antitoxin administration are reported.

We feel justified in concluding that the efficacy of sulfanilamide or azosulfamide against diphtheria is yet to be demonstrated.

Early administration of antitoxin in suspected and proved cases of diphtheria still remains the correct management.

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AN EASY-TO-MAKE INFANT INCUBATOR

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A PRACTICAL, automatic incubator for infants can be built at a cost of ten dollars or less. The incubator is a rectangular box equipped to warm and moisten the enclosed air.

The box is constructed of plywood, and screws are used throughout. Several coats of washable paint will protect the wood. The most practical measurements are 14 by 26 by 20 inches since the incubator will then fit into a bassinet frame and accommodate the standard bassinet mattress. The upper half of one side is fastened so that it can be opened to care for the infant, and the upper part of one end is left open to admit adequate fresh air. A single thickness of bedsheet may be used to close partially this end opening when necessary, either to raise the humidity or for administration of oxygen. This type of closure eliminates the danger of suffocation.

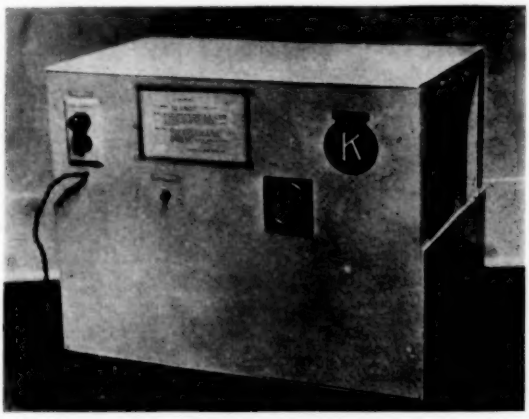

Fig. 1.—Exterior of incubator showing main switch, regulator key, and temperature-humidity indicator.

Sockets for three 40-watt light bulbs are attached along one side near the top of the box. The temperature is regulated by means of a thermostat intended for chicken incubators. This regulator has a snap-action electrical switch designed for 110-volt current and a load of 1,200 watts. It holds the air within 1° F. of any desired temperature and may be obtained from Sears Roebuck and Co. at a cost of $1.35.

Moisture is fully as important as heat if an incubator is not to become a "fireless cooker." The water container is constructed deep and narrow to minimize spilling—dimensions of 12 by 1 by 3 inches are satisfactory—and is mounted firmly against the upper portion of the closed end

From the Copper Queen Hospital.

of the incubator. An ordinary desk blotter is cut into a rectangle 20 by 10 inches and centered on top of a piece of copper house screen 24 by 12 inches. The extending portion of the screen is bent over the edges of the blotting paper to form a screen-enclosed "wick." One end of the wick is placed in the water container. The free end is suspended by means of two wire loops at the top of the box above the light bulbs. The copper screen not only protects the wet blotter but also disseminates heat rapidly to all portions of the blotter. Heat conduction will prevent ignition of the paper should it accidentally become dry. To prolong the usefulness of the wick, use only distilled water.

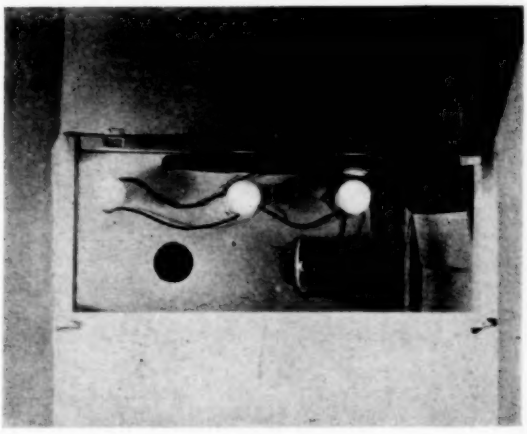

Fig. 2.—View with side open showing interior arrangement.

A combined temperature and humidity indicator (such as Airguide, Jr.) should be obtained and mounted over an opening near the center of one side, so that the air within the box reaches the vented back of the instrument.

The switch governing transmission of electric current to the incubator should have a pilot light. The following directions are attached to the incubator shown in the illustration:

To operate: Turn on main switch so that pilot light is burning.

Heat: Maintain temperature between 85 and 90° F.
To increase, turn regulator counterclockwise.
To decrease, turn regulator clockwise.
Allow sufficient time for stabilization after regulating.

Humidity: *Distilled* water should be added to hydrator every twelve (12) hours.
Maintain humidity above 50 per cent.
Regulate humidity by partial closure of open end of incubator with a single thickness of sheet.

Special Article

PLAY TECHNIQUE

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TO THE adult a child's play is a means of keeping him amused, contented, busy, and, when too occupied to listen to the child's chatter, an opportunity to remove him for the time being in an acceptable way by saying "Run out to play," or "Wouldn't you like to build with your new blocks, or play with your train?", etc.

To the child, particularly in the early years, play furnishes an outlet for many of his real feelings which he dares not express openly in the presence of adults, but which he phantasies in the guise of play.

When one remembers how different the child's world is from the adult world, a world for him walled in by "you may" and "you may not," at an age when he is too young to verbalize what his own feelings are or to understand what his own wishes are, and how much these wishes are colored by the inhibitions which the adult world has already imposed upon him, one observes play with a renewed interest and understanding of some of the reality experiences of the child's small and short life, a life which he is attempting to puzzle out and verbalize, not in words, but in action.

Who has not observed the child who has recently undergone a tonsillectomy, repeatedly performing the same operation on his teddy bear by cutting open the throat until the trauma of his own operation has completely worn off. The necessity of preparing children for operations, tests in the laboratory, etc., is no unexplored field to the pediatrist. For the most part, there is now no whisking away of the child to the hospital without warning unless it is an emergency and the child is too ill to profit by such a preparation. The shock and fear of the child following such a procedure are well recognized.

A little boy who had never been separated from his parents in his four short years was taken to a hospital and left overnight following a tonsillectomy. He was totally unprepared for the operation which was followed by a hemorrhage, which, although short in duration, was nevertheless terrifying to him, since his parents had left shortly after he seemed to be comfortably situated for the day. The nurse who cared for him was a stranger whom he had never seen before. Until the hospital experience he had been a constructive, independent youngster. Upon his return home, he insisted, for the first time, upon having a light in his room at night, refused to go to bed alone, and awakened

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frequently, crying out. It was also noticed that he complained for about six weeks of having difficulty in swallowing.

The pediatrist assured him that his throat was completely healed, as did his parents. Bribes and threats were of no avail; his refusal of food was steadfast. In play he presented an interesting picture. For three play periods he placed all the dolls in the playroom in various beds, covering their heads, saying they had "sore throats." When no effort was made to ask questions, he got them up one by one, saying they were getting better. As each doll was taken up, he gave it to the psychologist, asking her to dress the doll. Then began a series of imaginary tea parties, when the psychologist drank with relish and ate enthusiastically from empty dishes. Bobby watched wistfully and round-eyed, but took no part in the proceeding; he refused to let the dolls have a part in the party, saying, "Babies are sick, can't eat." On one occasion he entered in the party but refused to let the dolls eat.

At this time his speech was less infantile. His fifth birthday was approaching and there was some conversation about what happened when a little boy really became 5 years of age—a penny more allowance, kindergarten, etc. In this period it was noted that he suggested spontaneously having a party with the psychologist alone. When he was asked to name articles of food for the occasion, he said quickly, "Pink ice cream and chocolate cookies. I'll bring my own cookies." On the stated day he arrived with the cookies, brought the wooden family to the table, but quickly disposed of the mother and father under the table, saying in a loud voice, "They can't come, they will talk too much," which his own parents actually did in coaxing and threatening at the table. To the psychologist he said, "You can stay if you are quiet and don't look." He added an older boy and girl from the wooden family. (He is an only child.) All the dolls were excluded with the remark, "They are babies."

The psychologist, looking out of the window, waited for the next move on his part. He said, almost in a whisper, "You eat," which she did, being careful not to observe him too closely, comment on the food, or eat too rapidly. His food at first disappeared in gulps; then he ate noisily, but without comment from the psychologist. Finally he ate slowly, as if enjoying every mouthful, without talking. At the end, the psychologist said casually, "This was a good party. I am wondering how brother and sister enjoyed it." He said, "They did not eat enough, but they will next time." Bobby helped wash the dishes and clear up the party. No further mention was made of food, but in the end when he was given his regular appointment card, which he was helping to fill out, he said, "Maybe I'll come tomorrow and come alone." He was merely told that we should be looking for him. That night he remarked to his parents that the psychologist's food tasted better than any he had at home.

With some effort the parents were persuaded to allow Bobby to eat alone and to give him always small portions, leaving the initiative

to him to ask for more food. For several weeks Bobby ate only one serving, and then quite unexpectedly asked to eat with his parents. During this period, he was invited to lunch with the psychologist several times and allowed to select his own food. Sometimes his selection was that of the psychologist, but on several occasions he made his selection quite spontaneously and with good judgment. Within six months, in consultation with the pediatrist, it was decided that his period of treatment could be terminated.

This case probably illustrates very well what most pediatrists realize—that the pressure of the parents in constantly making food an issue when it was so closely tied up with Bobby's fears over his tonsillectomy, his "sore throat" following the operation, and his inability to verbalize his own feelings caused his symptoms to increase. His play in the presence of one who observed but refrained from comment gave him a sense of security to continue acting out his feelings until he no longer felt afraid of them. Perhaps the greatest stride was made when he volunteered to bring the cookies which were difficult to swallow, leaving the psychologist to provide what to him was the easiest task, the swallowing of the ice cream.

It has been the writer's experience that children, when allowed to select their own form of play, quickly bring out the phantasies which are of some concern to them. How often we have noticed great hostility worked out in "shooting games," aggressiveness in throwing balls with great force, wrecking trains filled with a wooden family. At such times children are either often careful to remove the "hated person" from the crash just in time or seem to gain some satisfaction in smashing such a person in their phantasy, exclaiming, "Now he is dead!" It is to be remembered that children are quite literal. When very young, they feel their smallness and uselessness in fighting the adult world which, to them, represents power. How often children are known to say of an adult who has perhaps rightly or wrongly frustrated them in gaining their own wishes, "I wish he were dead!" Death to them is not death in the true sense of the word, but merely removal of an obstacle to their ends.

A little 8-year-old boy, overprotected by both sets of grandparents and his parents, was given to frequent outbursts of temper. He was an only child in an adoring adult world. His adjustment to school was very difficult, particularly to a teacher (a mother substitute) who could not give her entire time to him, but must share it with thirty-five other boys and girls of his age. He found conforming to school rules especially difficult because "rules" in his home could always be changed for his benefit. Although he was a very intelligent boy, his work was never completely done and was considered, at best, of poor quality. His teacher was insistent that he could do better work and resorted to keeping him after hours to rewrite his papers, learn his spelling, etc. The first rationalization he offered was that he was "glad because he did not have to play with the other kids," of whom he was very critical.

His family noticed that he became very difficult at home, insisting on the smallest details being worked out for his convenience. He began finding excuses for not going to school, for example, "nausea, not feeling well, or headaches." At such times the family was even more protective and overanxious. One evening, when discussing his feelings with his paternal grandfather, he said, "I would be all right if I never had to go to school. I wish it would burn down and my teacher and every teacher in the world would die!" Within half an hour the fire alarms sounded in the small community in which he lived, and it was discovered that the school building was afire. He rushed from the house, was the first child to reach the fire, tried to rescue his belongings, and was particularly upset over the fact that the building was entirely destroyed. A substitute school situation was set up in another building and his fear that he had really caused the fire was shown early in his anxiety to arrive at school on time and his overanxiety to please his teacher and the other pupils. His work improved, but he became fearful of many things. He complained of "bad dreams," began sleepwalking, etc.

It was at this time that he was sent to the psychologist. His treatment was interesting. He would not discuss school, although this episode had happened almost two years previously. He began by drawing pictures of such things as boats, and airplanes, always remarking that he "would like to fly in the sky or sail a way off." Then he drew a series of houses and gradually began drawing school buildings, large and spacious. Eventually, with a little help, but with much fear expressed on his face, he told the story of how he had early felt about school and still felt, although he never "told anyone." Then came his real fear that his grandfather had told what he had wished and how perhaps, as a punishment, he might be sent to a "reform school." He said everybody would "dislike him." "Do you think I started the fire and that is why Miss A. left?" (She had resigned for a better position the year following the destruction of the school building.) "I didn't really wish she would die." The drawing continued, with a constant talking out of his own feelings for a number of hours. Each time, the psychologist attempted to give him a better understanding of himself, his place in the family, and why he had disliked school to such an extent. His symptoms disappeared and, with the building of a new school, he began slowly to enter into the new activities, taking much pride in his particular room. His teacher, a very understanding and intelligent woman, gave him added responsibilities, helping him to work up to his own level by reassurance and some recognition of his work. The healthy note in his treatment was that at times when he felt particularly irritated at school or his teacher, he could come out with his feelings frankly to his teacher and his family. By this time they had gained some insight into the situation and could help him evaluate his own part in the momentary irritation which he felt.

Children who are trained too early in their toilet habits or handled badly in their training find much satisfaction in playing with clay,

water in sandboxes, etc. To one who is skilled in play technique, this makes an excellent opportunity to allow children to work out their real feelings which parents have hitherto regarded as taboo and forbidden. This very attitude may have caused the children to react with symptoms such as soiling, wetting, etc., many times during the day, refusing to indicate their toilet needs. Punishments of parents by these symptoms are well recognized.

Stories and poetry written by children are another outlet for their phantasies and real feelings. These are of immeasurable value when used as an interpretation of the child and his problems.

Toys regarded so lightly by adults as interesting or attractive cannot have the same meaning to the child. Too often new toys are cast aside by the child in preference for older ones which have a special satisfaction to him because he has a security with them, battered and worn out as they may seem to "grownups."

A small boy, Peter, 5 years of age, very average in intelligence, had as a sibling a brilliant little girl 10 years of age, who was especially liked by everyone. Peter was referred to The Children's Center because his temper tantrums and constant hitting of other children were such upsetting factors in the kindergarten that the school advised that he be excluded until he had learned to play with youngsters. On Peter's first visit, it was noted that he carried a large parcel clasped closely to him. He did not volunteer to disclose the contents of the parcel, but it was observed that he kept it near him, showing some fear that it might be lost. Subsequent observations disclosed that it was a worn, large teddy bear, grotesque in appearance because of the absence of one eye, torn paws, etc. It was first wrapped in newspapers, then a blanket, and over all the other wrappings was his father's sweater. It was some time before he began to uncover certain frustrations which he felt in his family, his sister's being the center of attention with his parents, grandparents, and other relatives, her having more privileges, etc. At that time he began peeling off the wrappings of the teddy bear one at a time. It is of especial interest that he always said, "My teddy bear thinks this," or "He doesn't like Nora [the maid]. She is rough and throws him around," but never did he say, "I don't like my sister or the maid."

The day came when he brought the teddy bear entirely stripped and said to the worker, "You hold him, I want to visit with you." This toy had been of the greatest security to him, because his parents, who thought of his attachment to it only as an infantile proceeding far below his age level, said frankly they often heard him talking to the teddy bear. In fact, he always took it out with him to play and to school if he were not "caught in time."

As treatment progressed, Peter began voicing his own protests in the family, and the family was made aware of his need to be heard, although his conversation seemed trivial to them. The sibling also was given a

better understanding of Peter and his slowness, as against her rapidity in action. She probably became the most therapeutic agent in the family, inasmuch as she became a constructive older sister to whom he soon learned to go with his problems, being sure of an understanding which he had not before received.

To him the psychiatric social worker was never-failing, interested always in the smallest details of the happenings of his day, and quite different from his father, who resembled the daughter very much in appearance and who spoke always in a sure, quick manner, only half listening to the conversation of others. Peter is now well adjusted at 6 years in a small schoolroom of children of average intelligence. He takes great pride in his work and has been promoted to the first grade.

To play with children and from them to learn their very thoughts and feelings can be done only when the adult becomes a quiet, silent, sympathetic listener, always on the alert for any response, however seemingly trivial, whether it be in verbalization or in actions. The child is aware of those "grownups" who go to make up his world. That he is can be seen in his play, his writing, if only an offering of a few lines. Hughes Mearns, the writer of many books in creative education, quotes the following three-line poem which was offered to him after four short years of a little girl's life experience:

> "Father takes coffee,
> Mother takes tea,
> Nobody asks me."

Here was a perfect expression of her feelings toward her place in the adult world. A small daughter of a very busy physician, in playing house one day, straightened and rearranged the furniture in the dollhouse to her satisfaction. She looked over the wooden family carefully, throwing the "father" doll into the attic and closing the door tight. When asked rather cautiously if there was to be no father, she shook her head emphatically "no" and said, "He never pays attention to his boys and girls. All he does is telephone and run"—a good picture of her feelings toward her father. Little could she, at that age, appreciate the seriousness of her father's profession or his hurried verbalization as he left the house.

As adults, we have much to learn from children about their true feelings, constructive and destructive as they may be, particularly before these feelings have been repressed and mechanized by the culture into which they are born and will eventually grow to adulthood. Shall these feelings be frustrated until the children become unadjusted to their reality because they cannot understand their own mechanisms of behavior or those of the people with whom they come in daily contact, or rather shall these early feelings be recognized and handled wisely, leading the children ultimately to constructive and adequate adulthood?

American Academy of Pediatrics

Proceedings

NINTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

CINCINNATI, OHIO—NOVEMBER 16-18, 1939

Round Table Discussion on Diarrhea and Dysentery

Chairman: George M. Lyon, M.D., Huntington, W. Va.
Assistant: Horton Casparis, M.D., Nashville, Tenn.
Secretaries: Matthew Winters, M.D., Indianapolis, Ind.
Benjamin Hoyer, M.D., Cincinnati, O.

CHAIRMAN LYON.—Two points which I desire particularly to emphasize are (1) the need for a better understanding in regard to the significance of diarrheal disorders and (2) the fact that the important diarrheal disorders are in one way or another preventable.

Diarrhea should be considered as a symptom, and not as a disease entity. At times, however, the diarrhea and its accompanying complications of fluid imbalance, acidosis, etc., may so dominate the picture that the initiating factors are lost to our attention. Diarrhea may be a symptom of clinical conditions initiated by widely different causes. I have prepared an outline for this discussion, which, in a general way, groups the diarrheal disorders in accordance with related initiating factors.

Diarrheal Disorders Grouped According to Related Causes

1. *Infections of the gastrointestinal tract* (particularly those caused by *B. dysenteriae, B. typhosus, B. paratyphosus, Salmonella suipestifer,* amoeba, vibrio cholera, etc.).

2. *Diarrheal disorders possibly due to virus infections of the gastrointestinal tract or secondary to a general systemic virus infection.* (It is possible that many of those placed under section 4 as due to reduced digestive function secondary to parenteral infections should be placed here.)

3. *Diarrheal disorders from ingestion of food contaminated with bacteria, molds, etc.,* in which, as a direct result of their growth within the food, true toxins are found. These bacteria and molds in themselves generally are not pathogenic in small numbers in the intestinal tract. The toxins may be a part of their bacterial bodies or arise as a result of their growth within the food and be exogenous in character. Staphylococci, some of the coliform bacilli, and *Salmonella aertycke* are notable offenders in this type of disorder.

4. *Diarrheas resulting from reduced digestive functions* whether from parenteral infections, chilling of body, overheating, humidity—air temperature relationships, etc., and which are said generally to be characterized by a decreased amount or

concentration of digestive juices and/or impaired assimilation from the intestines and/or resulting incomplete digestion of ingested food. (This group seems to be decreasing in incidence and in importance.)

5. *Diarrheas from ingestion of intestinal irritants* such as green apples, corn, bran flakes, laxatives, poisons causing diarrhea, etc.

a. chemical
b. mechanical
c. mixtures of chemical and mechanical

6. *Diarrheas from overfeeding.*

a. Simply ingestion of too much food unaccompanied by other influences
b. Ingestion of too much carbohydrate in unbalanced diet (?)
c. Ingestion of too much fat in unbalanced diet (?)

7. *Allergic diarrhea*

8. *Nervous diarrhea*

9. Form of *"eliminative" diarrhea* seen in uremia and acidosis from the excretion of endogenous toxins in the intestines.

10. *Starvation diarrhea*

11. *Diarrhea from gastrointestinal bleeding*

Between the diarrheal disorders of the purely infection type (section 1) and those of the purely irritation type (sections 5 and 6), there are all manner of gradations and mixtures of intervening forms.

It might be best to group the diarrheas due to food contaminated with growth of bacteria and molds (section 3) under those due to ingestion of intestinal irritants (section 5), were it not for the fact that these food infections need emphasis as a preventable cause of diarrhea.

Pediatricians should endeavor at every opportunity to aid in the promotion of a clearer understanding of these conditions, a simplification of their treatment, and a rational program directed toward their prevention.

Pediatricians and public health workers living in the southern and southeastern states have been familiar with bacillary dysentery for more than twenty-five years and have recognized it as a common important form of infectious diarrhea. It was not until after the Third White House Conference in 1930 that bacillary dysentery became an accepted disease entity among a great many of our pediatricians. With increasing frequency, reports of true bacillary dysentery, confirmed by obtaining positive stool cultures, have appeared from those pediatric clinics where none had been recognized previously. In West Virginia there has been a very remarkable decline since 1933. A few years prior to this, the Sonne type of dysentery bacillus was recognized as a relatively frequent cause of dysentery. With unusual frequency the Sonne type of bacillus is recovered from stools presenting only pus and mucus, and not containing blood. The Sonne type is much more widely prevalent than is generally recognized, and probably accounts for a large proportion of the cases from which characteristic cultures of *B. dysenteriae* (Flexner) are not obtained. In our regular experience, (1920-1930), the Flexner strain accounted for 80 per cent of all the cases we studied by stool cultures. Of the 20 per cent we were not able to classify at that time, the majority probably were of the Sonne type. I have encountered the Shiga strain on only three occasions, and in each instance the patients had come from the vicinity of Memphis, Tenn., where Mitchell has reported the frequent finding of this strain. We rarely encountered the Shiga strain in Baltimore during the period from 1918 to 1923. The Flexner bacillus can at times produce a clinical picture of such severe toxicity that it closely simulates the Shiga form which is characteristically much more severe in its clinical manifestations, and much more fatal in its final outcome.

Since 1930, reports of a wider prevalence, or at least a wider recognition of bacillary dysentery as confirmed by stool culture, are observed in the literature. Whether this represents an actual increase due to increased means of communication to and from endemic foci of infection, such as the mining areas of my own state, or whether it is simply due to more accurate observation and recognition, cannot be determined easily. Certainly there has not been a significant increase in the infant diarrheal death rates in the centers from which these reports have come.

Of particular aid to a better understanding of the diarrheal states has been the application of more careful techniques of stool cultures. There has been a gradual increase in the relative percentage of the infectious diarrheas as compared with the noninfectious. It has been most interesting to observe the decrease in the so-called noninfectious diarrheas which, over a period of years, inevitably parallels a decrease in the truly infectious diarrheas. Hoyer, Cooper, and their associates have observed a striking similarity not only in the incidence, but also in the factors which influence the incidence, of the apparently noninfectious or stool culture-negative gastroenteritis cases as compared with those of the infectious or stool culture-positive cases. We know to some extent how to prevent the obviously infectious cases. In doing so, we will bring about a reduction in the total number of cases of diarrhea, both infectious and noninfectious. This point, I feel, warrants great emphasis. The fact that there is a corresponding decrease in the so-called infectious or simple diarrheas in those states or communities where bacillary dysentery is brought under control is important. We are forced to accept the fact that undoubtedly more of our cases of apparently simple gastroenteritis are in reality infectious with organisms unknown to us or unrecognized. The cycle of incidence through which these infectious and noninfectious diarrheas go is interesting and not at all understood. In West Virginia, the incidence of bacillary dysentery as measured by the diarrheal death rates in patients under 2 years of age have been reduced since 1933 to approximately one-third of what it had been during the preceding ten years. Public health endeavor more than pediatric effort has brought about this reduction.

I have previously recorded how impossible it is within a community in which dysentery is endemic to prevent a child from becoming infected with the dysentery bacillus when prevention is forced to depend solely on such individually applicable measures as boiling milk and water, proper selection, preparation, and protection of food, and individual attempts at fly control.

Where community sanitation is inadequate and flies have access to contaminated excreta, the excessive incidence of dysentery will vary in relation to the total fly population. Whether the fly carries diarrhea-producing organisms other than the dysentery bacillus, one does not know, although this seems likely. We have made other observations which indicate that periods of excessive rainfall, by drowning the larvae and the pupae and by killing and hindering migration of the adult fly, are accompanied by a relatively low incidence of fly infestation and a correspondingly low incidence of bacillary dysentery. This probably explains the earlier seasonal peak for dysentery in the southeastern states, where soon after May and June the summer rains appear and probably exert a similar inhibiting influence on the life cycle of the fly. Periods of extreme prolonged drought are accompanied by a smaller fly population, again undoubtedly due to conditions adverse to the survival of the larvae and pupae, and perhaps of the adult fly as well. We have found that both excessive rainfall and excessive drought tend to favor a low dysentery incidence in communities having inadequate community sanitation.

Fig. 1 is a diagram of the relationship which the housefly bears to the spread of dysentery. There would be relatively little dysentery among infants or young children if all human excreta, including the very important diarrheal diaper, were adequately protected from fly contact. However, hand-to-mouth infection, whether

direct or indirect, accounts for a rather constant proportion of dysentery cases. But it is rare for the disease to be spread by means of either milk or water as typhoid is spread. While typhoid bacilli are spread both by flies and by food and water, one does not find a parallelism in the spread of dysentery bacilli. While dysentery bacilli are readily cultured from the feet and intestinal tract of flies which have had recent access to dysentery-contaminated excreta, there are on record very few instances of proved milk- and water-borne infections.

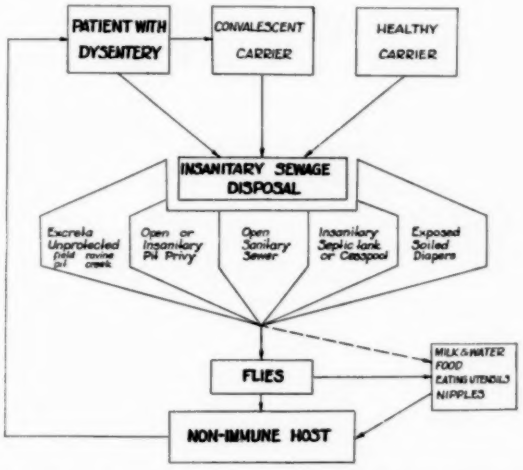

Fig. 1.—Diagram showing common role of the fly and insanitary sewage disposal in the spread of bacillary dysentery.

The common housefly has a much greater ability to spread dysentery bacilli than the stable fly or other biting flies. The common housefly, or *Musca domestica*, has mouth parts that are peculiarly adapted to the situation. There is a hollow tube or proboscis which is soft and can be used for sucking, but not for biting. The esophagus, proventriculus, and the ventriculus are connected with this amazing sucking apparatus which, in turn, resembles somewhat the trunk of an elephant. By means of this handy organ, the fly busies himself depositing saliva, and then by alternately sucking and puking the fluid media it contacts, it exercises its most important mechanism for obtaining live bacilli from contaminated excreta, diapers, etc., in order that it may transfer them in a viable state to the food, fingers, lips, etc., of the infant or child. The little fly specks with which you are familiar are made otherwise than in the manner you would expect.

We break the cycle, as is shown in Fig. 1, either by limiting sufficiently the number of flies, which is admittedly not easy to do, or by providing adequate community sanitation and diaper control, which, while not any too easy of accomplishment, can be done. How rarely are patients with infectious diarrhea properly isolated? What a tremendous number of cases of apparently noninfectious diarrheas must in reality be infectious! Are these isolated and screened as they should be? How very true it is, indeed, that we should regard all diarrheal stools and all soiled diapers just as much of a bad sanitary hazard until properly cared for as other forms of imperfect or insanitary sewage disposal.

I am tempted to tell of an interesting observation which was recorded many years ago. These observations were made at a prominent summer resort in the southern part of England, back in the old typhoid days when the only sewers were

nothing but half-open gutters, and the pit privy was the more refined form of toilet disposal. It was a very common practice for wealthy folk to go to this resort on the southern shore of England because it was known to be particularly free from diarrheal diseases, including the "bloody flux" and the typhoid fevers, particularly during those seasons of the year that other parts of England had their usual summer and fall excesses. During this season of the year, when flies were generally most plentiful in other places, there was a strong breeze from the sea which blew inland, and it undoubtedly took with it the flies from this resort. This must have been the explanation for the fact that flies were not seen at this resort and that the resort actually had a low incidence of gastrointestinal infections. It is said that one did not have to go very many miles inland before the expected incidence of these intestinal diseases and flies were encountered. The influence of wind movement has been noted on more than one occasion with regard to the appearance of mosquitoes and malaria. There are few instances where the relation of wind movement to dysentery is so perfectly demonstrated as at this seaside resort, and this despite the fact that there was insanitary sewage disposal and undoubtedly a certain number of carriers more or less constantly present within the community. With all this, there did not occur the excessive incidence characteristically found farther inland.

While I may have seemed to overemphasize the importance of prevention of diarrheal disorders, I have done so because it is through the proper recognition of these facts that one can expect to approach the problem of prevention logically.

Referring again to the outline listing the various types of diarrheal disorders, it becomes obvious that not all cases with diarrhea as an important symptom may be prevented in the manner I have just discussed; namely, the control of sanitation and the prevention of flies. It is quite as obvious that the prevention of diarrheal disorders will demand a variety of widely differing methods of approach, depending upon the particular initiating factors. Fortunately, from the standpoint of therapeutic management things are somewhat more simple, for, in general, the treatment of most diarrheal disorders is fundamentally much the same, outside of the management of the initiating cause, and there are many ways of achieving the same successful end result if certain fundamental principles are followed.

In general, the treatment of diarrheal disorders may be summed up in the following topical manner:

1. Removal or correction of precipitating factor where possible
2. Rest for the gastrointestinal tract for an appropriate period
3. Gradual return to a normal diet qualitatively as well as quantitatively
4. Combat against fluid loss and dehydration from the start.
5. Close observation of all cases and avoidance of extremes of therapy

DR. CASPARIS.—I will limit my remarks to those diarrheal disorders looked upon as not being infections of the gastrointestinal tract. While I cannot agree entirely with Dr. Lyon's outline, there are certain gross divisions which can be made somewhat in accordance with his suggestions. Before I go on with my discussion, I would like to ask Dr. Lyon to tell us something about an experience he has recently had with so-called epidemic diarrhea of the newborn infant.

CHAIRMAN LYON.—In August, 1938, we observed an epidemic of diarrhea of the newborn infants in the nursery of a general hospital. This was the third such epidemic which we had observed in this same hospital. No dysentery bacilli or other pathogens could be cultured from the stools. A great many times we have observed dysentery bacillus during the neonatal period. Because of this, we were quite familiar with the clinical picture of *B. dysenteriae* infections in this age group. As we have seen it, there is little similarity between epidemic diarrhea of the newborn infant and *B. dysenteriae* infections of the newborn infant.

At the time of each of the three epidemics observed, there was within the community a remarkably high incidence of acute epidemic influenza and a high death rate from respiratory disease among infants. Grippy febrile illnesses with leucopenia and roentgenographic shadows indicative of atypical pneumonia or pneumonitis, as well as occasional post-mortem findings suggestive of influenza virus infection, were more prevalent than usual at these times (December, 1926, October, 1934, and August, 1938).

The difficulty of preventing such epidemics, particularly within the newborn infant nurseries of general hospitals, is emphasized by our observations. The mother of the first baby to be attacked had suffered from a grippy illness, with a low-grade fever, malaise, and respiratory distress, the week prior to admission. No attention was paid to this at the time. She was given a private room. Her newly born son was brought to her from his bassinet in the general nursery every four hours to nurse and was then returned to the nursery. Suddenly, on his sixth day he became ill with fever, convulsions, and loose stools. The second case appeared forty-eight hours following onset in the infant in the adjoining bassinet. Just forty-eight hours after this, three more babies came down with a similar clinical picture, and then for the first time it was quite obvious what was taking place. The explosive invasiveness of the epidemic, the clinical observations of the patients, and the post-mortem findings combined to provide us with an opportunity for most interesting observations.

The infants who were severely ill and those who died presented evidences remarkably suggestive of intracranial difficulties. At autopsy an extremely severe cerebral edema was found in each instance, and also many minute hemorrhages in the cortex, but no gross bleeding at any point. Although there were remarkable changes in the intestines, they did not suggest at all those of a dysentery infection. There were evidences in microscopic sections of the hyperplastic mesenteric lymph glands and of the lungs suggestive of a virus invasion which was uncomplicated by secondary bacterial infection. One of the infants presented a characteristic influenzal pneumonitis not accompanied by secondary bacterial invasion. None of the pathologic sections were at all suggestive of bacterial invasion.

Three extremely ill infants, with temperatures in excess of 105° F. and with convulsions, cyanosis, dyspnea, and extreme prostration, all of which developed too early to have been brought on by dehydration from diarrhea, and who did not show any evidence of acidosis, were treated with citrated whole blood received from a person recently convalescent from an attack of acute epidemic influenza. Their immediate response was remarkable; their temperatures fell rapidly, their clinical improvement was unmistakable, and their recoveries were uneventful. To several of the other infants who were critically ill, all but one of whom died, transfusions of citrated whole blood were given or citrated whole blood (normal, not convalescent) was given without similar benefit. This experience is full of interesting implications, but certainly no conclusions can be drawn from it. My associates and I naturally will be inclined to attempt the use of convalescent influenza whole blood or serum should we ever find ourselves in a similar situation.

The clinical picture and the epidemiology of these cases correspond very closely with the most severe cases reported from New York City by Frant and his co-workers.

Epidemic diarrhea of the newborn infant may not be a separate and distinct clinical entity. However, there is a relatively characteristic incubation period which suggests that, at times at least, closely related incitants may be responsible for those cases which correspond with those we have observed, and with those observed in New York. In this rather characteristic picture, the incubation period is approximately six days; there is an absence of the ordinary evidences of bacteriologic invasion, and bacteriologic studies, both ante mortem and post mortem, are

essentially unrevealing; there is a high death rate, death occurring generally between the ninth and fourteenth days.

From the many varied descriptions of diarrheas of the newborn infant which appear in the literature, it would seem that there are other types of diarrheal disorders which may occur in the newborn infant, which may be confused with this more or less characteristic clinical picture, and which may be caused, not by a specific or related factor, but by other organisms known to produce diarrheal states in older people. The cases of general sepsis described by Blatt should not be confused with those found in these epidemiologically characteristic instances. It seems quite probable, in some epidemics at least, that the specific incitants of epidemic influenza or other closely related respiratory viruses may be responsible for the clinical picture referred to as epidemic diarrhea of the newborn infant. There are some references by von Reuss and others which indirectly suggest that perhaps during periods of influenza prevalence, such outbreaks may have been observed and also that such cases may have been seen and were considered to be cases of general sepsis. Indeed, it seems quite likely at times when general sepsis of the newborn infant was more frequent than in recent years that the occurrence of outbreaks such as we have recently observed may have occurred and were not properly recognized as such. It would seem, however, to be a disease which has appeared most characteristically, in its clinico-epidemiologic expression, since the widespread use of hospitals by obstetric patients. Personally, I believe I have seen the same disease in a milder form in newborn infants born at home during the 1918 influenza epidemic and on occasions of influenza prevalence since then.

Little is known about virus infections or their behavior in the newborn infant. Little is known about the immunologic responses of the newborn infant to either bacterial or virus invasion, and yet it is not at all unlikely that some of the viruses which commonly produce the primary phase of our respiratory disorders may, when implanted on the susceptible newborn infant, produce a picture such as that we now describe as epidemic diarrhea of the newborn infant.

DR. CASPARIS.—In his outline, Dr. Lyon suggests an extremely important and poorly understood source of diarrheal disorders which may at times be extremely serious. Curiously enough this condition may be accompanied at times by the appearance of blood in the diarrheal stools, although pus and mucus, as seen in the stools of true bacillary dysentery infections, rarely occur. I refer here to those cases of food poisoning with which the public health workers seem to be more familiar than are we practicing physicians. There is an interesting collection of literature on this subject in the public health journals. Dr. Lyon could tell you, if he would, about an experience where chicken was cooked, left overnight at room temperature, made into chicken salad, and served at a Sunday supper the following evening. Approximately two-thirds of the guests at the supper party became acutely ill with vomiting, diarrhea, and prostration within from two to three hours after eating the salad. Such instances occur not infrequently and are generally referred to as "ptomaine poisoning." As a rule, they occur because of just such a break in the technique of protection and preparation of food as occurred in this instance. Bacteria of various sorts may be responsible for such food poisoning, and the manner of their entry into the food may be most bizarre. Sometimes the bacteria which multiply in food which is allowed to stand are staphylococci, and at other times, some of the *Salmonella*. In fact, many different types of bacteria have been incriminated at one time or another, and even molds have been known to produce such a chain of symptoms.

One practical point to be drawn from this is that we should insist upon careful attention to the preparation and protection of a child's food. The toxins from such food-contaminating bacteria are extremely virulent and are generally heat-stable.

DR. M. L. COOPER, CINCINNATI.—The Stone test of toxin-producing staphylococci is a method based on the observation that only the toxin-producing strains of staphylococci liquefy gelatin media when prepared after this method. A Bacto-Stone's extract gelatin agar may be used for the test. It is not a chemical test for the toxin within the contaminated food.

DR. CASPARIS.—The term "ptomaine poisoning" is frequently used for such cases. It is very rarely, if ever, that such instances are true ptomaine poisoning. The ptomaines are even more powerful toxins and occur under vastly different conditions.

It is well to recognize the importance of this group of cases, and while we do not see them frequently, the fact that they may simulate other types of poisoning or infection makes it worthy of our attention. I would like to ask if diarrhea can result from bacteria contained in food or in milk even after they have been killed by cooking or by pasteurization.

CHAIRMAN LYON.—It is quite likely that many cases of acute gastrointestinal upsets, including vomiting and diarrhea, are due to the ingestion of milk containing the dead bodies of bacteria with their associated toxin. This particular toxin is very heat-resistant. We have seen clinical instances which would verify this belief. In the pasteurization of milk it is desirable that the milk be clean and that it be pasteurized as soon after milking as possible, and that from beginning to end it be protected against contamination.

DR. CASPARIS.—It is in this latter part of Dr. Lyon's outline in which I think we run into the greatest dissension and hear the widest variety of opinions from those interested in the subject. I am referring to that part of the outline which concerns the large variety of conditions in which diarrhea appears as a symptom, but conditions which are broadly thought of as the noninfectious type of diarrheas. In connection with this ill-defined group, I feel that we have certainly undergone a change in viewpoint in the last twenty years. At various times we have blamed overfeeding, proteins, carbohydrates, and fats for most of our troubles. Certainly, simple overfeeding does not hold the place now that it once did as a cause of diarrhea, nor do proteins, carbohydrates, and fats seem to me to play the prominent part in the production of diarrhea which was once attributed to them. Likewise, chilling of the body, overheating, humidity—air temperature relationship, etc.—do not seem now to have a very prominent place as causative factors. Still, dietary indiscretions such as eating green apples or corn, or taking laxatives, etc., can produce digestive disturbances with diarrhea as a symptom.

In the case of the majority of these "noninfectious diarrheas," for simplicity's sake and for the sake of a practical approach to treatment, I find it easier to think of them as *irritations*. I say irritations because, although infections of the intestinal tract produce irritation, there seem to be many other means by which the tract becomes irritated and peristalsis increased, with a resulting diarrhea, or at least frequent bowel movements, in which one can find no definite evidence of infection on post-mortem examination of the tract.

Belittling simple overfeeding as a cause of diarrhea should not make us forget that under many circumstances, such as parenteral infections, probably extreme hot weather, etc., digestion becomes definitely impaired, and previously normal feeding may be overfeeding under these circumstances. In other words, when one suspects that there is any condition that might impair digestion, one immediately quantitatively or qualitatively reduces feeding.

To elaborate a little further on proteins, carbohydrates, and fats, proteins have largely been given up as a cause for diarrhea except in the case of specific irritations, which will be discussed under allergy. Carbohydrates, in my opinion,

cause a great deal less trouble than we used to think. In my experience, it is extremely rare to find any trouble from any one of the carbohydrates or sugars which we commonly add to the various milks to make the carbohydrate content approach that of human milk. If one varies much from the sugar content in breast milk and goes to extremes in the addition of sugar, then I believe we might see some trouble.

One probably must pay a little more attention to fat when the digestive tract is sensitive, because in our own periods of sensitive digestion we subconsciously avoid fats. Likewise, I think it is true that the premature infant who has an extremely sensitive digestion does much better on skimmed or partially skimmed cow's milk than he would on whole cow's milk.

Previously, when we gave so much credit to these various elements of food as causes of trouble, I think much of it came from unclean or contaminated food and the attempt of parents to force the child to eat his regular diet during impairment of digestion associated with various illnesses, teething, etc. There has been a great improvement in the production of better quality foods, just as there have been great strides in the education of parents to insist on clean and wholesome food, to avoid overfeeding during impaired digestion, and to pay more attention to the preparation of the infant's food and to what goes into his sensitive gastrointestinal tract.

There is one aspect of irritation mentioned above which I think is often overlooked, and that is the irritation which not infrequently comes from the ingestion of foods to which a child, who belongs to the allergic group, is oversensitive. Under these circumstances one rarely finds what is really a diarrhea, but one often sees frequent bowel movements, sometimes large, sometimes very small, and often containing mucus. The passage of gas from the bowels and the symptoms of cramping or true colic are frequently associated with such situations as these, and in their management one attempts to change to a preparation that is not irritating to the tract. If the condition is not severe, occasionally evaporated milk, buttermilk, dried milk, or others of the specially prepared milk group might suffice. The change to goat's milk in some of the more severe cases occasionally gives complete relief from symptoms. The pylorospasm one often hears of certainly occurs on this basis sometimes.

As to the nervous diarrheas, this is a term about which we pediatricians probably do not have to bother. I have known certain adults, however, who are convinced that it is a good term and has real significance.

Starvation diarrheas may be seen occasionally. Rather than diarrhea, I would say that under these circumstances one is more likely to see frequent small bowel movements with little or no fecal content. Such a picture was much more frequent in the days when laxatives were commonly used, and when food was strictly withheld over long periods of febrile or diarrheal illnesses.

There is another so-called toxin which can maintain a diarrhea or frequent bowel movements long after the provocative cause has disappeared. This so-called toxin, namely, guanidine, which is present in small amounts normally, appears secondarily in the blood stream in toxic amounts most often when there has been acute and rapid dehydration, either from limited intake or increased loss of fluids, or both. The giving of calcium under these conditions is indicated since guanidine and calcium are physiologically antagonistic, and the toxic effects of guanidine can often be neutralized by the administration of calcium during an acute and rapid dehydration. This same toxic substance also appears when there is a good deal of damaged body tissue and commonly reaches toxic levels in the presence of superficial burns.

There are still other conditions which frequently are conducive to the maintenance of diarrhea or frequent bowel movements. One is nutritional edema usually resulting from low serum protein. Even a deficiency of vitamin C may

retard recovery when stress comes from illness. These latter statements imply that stress should be placed on the importance of maintaining good nutrition to avoid our having an impaired nutritional background to work with when illness does come. This is extremely important because no properly fed child will have a low serum protein or a vitamin C deficiency, but if intestinal upsets do occur, then our chances of restoring health quickly or of preventing prolongation of trouble and serious after effects are greatly enhanced.

I have emphasized these factors of guanidine intoxication, low serum protein, and possible vitamin C deficiency, because the first two, and probably all, of these defects impair the ability of the blood vessels to hold fluid and other essential elements in the blood stream necessary to maintain good circulation.

DR. B. W. CAREY, DETROIT.—In our experience in Detroit with epidemic diarrhea of the newborn infant, we found that on the "charity side" of the hospital the infants did well, whereas on the "private pavilions" they did poorly and many died. We believe the private cases brought in the infection. It is possible that they may have been influenzal infections. We feel that by watching the nose and throat in these cases it has been possible to reduce the extension of an epidemic.

DR. W. F. BURDICK, WASHINGTON, D. C.—Is it necessary to empty evaporated milk from the tin cans once they have been opened?

DR. CASPARIS.—I see no danger in leaving milk in the can as long as the exterior of the can is kept properly clean and is protected from flies and the milk is kept at a proper refrigeration.

DR. M. M. MILLER, AKRON, OHIO.—I rather question the validity of making a classification of diarrhea as to infectiousness or noninfectiousness on the basis of the appearance of the stools. This should be based on cultures only. Every winter we see a type of diarrhea in which the stools are from pale yellow to white, watery, with no pus or blood, and the patients may have some pharyngitis. There is generally a low white blood cell count. We have been calling these cases "intestinal influenza."

CHAIRMAN LYON.—It is impossible to classify these diarrheas accurately with regard to infectiousness or noninfectiousness. From a practical standpoint, it is desirable to consider all diarrheal stools as infectious; and in order to prevent their spread, the diaper and the stool should be treated as if they contained dysentery bacilli. But frequently we will be correct in assuming that the dysentery bacillus can be recovered from a stool if the stool is loose and contains blood, mucus, and pus, particularly the latter. In the winter type of diarrhea to which you have just referred, one rarely sees any pus. There may be green mucus, but the stools are, as you described, loose, yellowish to whitish in color, and may contain some mucus. Formerly, particularly from 1919 to 1926, we talked of a gastroenteritis due to pharyngitis or other parenteral infection. This is what occurs frequently during periods of respiratory infections. We also see the cases every August, although they are almost never confused with true bacillary dysentery. The term "intestinal flu" is not a good one, but we have diarrheal disorders, even in our older age levels, which are due to virus infections. Whether the virus stays in the respiratory mucous membranes, or circulates in the blood, or invades the gastrointestinal mucosa, is not known. The epidemiology of these cases, and the clinical expression strongly suggest this.

In general, the diarrheas due to irritation of the gastrointestinal tract are usually watery, have no characteristic color, may have some mucus, but rarely contain pus or blood. Occasionally a bloodstreak may be seen, but they do not begin to approach in either amount or character the blood, or blood, pus, and mucus which is seen in bacillary dysentery.

In dysentery convalescents, it is possible to demonstrate the agglutinins in the blood with amazing regularity, even to several months or a year after the acute infection. Newborn infants do not develop the agglutinins for *B. dysenteriae* easily. We have seen them fail to develop the agglutinins, although we had recovered organisms from their stools during their neonatal period. It is a mistake to fail to recognize infections due to the dysentery bacilli just because we are not getting positive cultures. Experiences show that we can get positive cultures in direct proportion to our patience and our interest. The workers in the average clinical laboratory will not do a good job of getting positive cultures from the stools. As I have said before, in the Sonne type of dysentery, frequently no blood may appear in the stools.

DR. LENORE PATRICK, WASHINGTON, D. C.—Are you using calcium in parenteral diarrhea where the serum protein is low?

DR. CASPARIS.—Of course, our first responsibility is to elevate the serum protein by blood or serum transfusion, supplemented by good diet, and I would at least give calcium if there were acute dehydration.

CHAIRMAN LYON.—I present here a brief outline of the important things to do in the treatment of bacillary dysentery.

Treatment of Bacillary Dysentery

Case of Average Severity:

Even the mild cases should be so treated.

1. Keep patient in bed until afebrile, stools of nearly normal character, and some degree of strength regained.
2. Force water, sweetened tea, or 5 to 10 per cent glucose solution by mouth up to 1,000 to 2,000 c.c., keeping record of intake which quite naturally depends on size.
3. For food, permit only whole cultured lactic acid milk every four hours, beginning with 2 oz. at a feeding. This may be increased by 1 oz. each day thereafter. Toward the end of the first week, add scraped beef, then custard made without egg yolk, then cottage cheese, Philadelphia cream cheese, and plain jello. Then add cream of wheat and potato, in the order named. Following this, add bread, rice, etc., and last of all, green vegetables, fruits, and roughage.
4. Continue oleum percomorphum, ascorbic acid, and thiamin chloride throughout.
5. Drug therapy:
   a. Give no laxatives as they only increase fluid loss and prostration.
   b. Phenobarbital for restlessness.
   c. Paregoric or deodorized tincture of opium for tenesmus.
   d. Five per cent cocaine ointment or 4 per cent tannic acid ointment for rectal comfort.
   e. Enemas not helpful.
   f. Bismuth, kaomagua, etc., harmless but not helpful.
   g. Local treatment for excoriations of buttocks as for intertrigo.

Case of Unusual Severity:

1. Hospitalize if possible and follow with best laboratory facilities available.
2. Keep careful record of
   a. Fluid intake (2,000-3,000 c.c.)
   b. Urinary output
   c. Character of approximate volume of stools in twenty-four hours
   d. Vomiting
   e. Unusual breathing or stupor

3. Protection of fluid balance
   a. Orally
      Water
      Physiologic saline
      Saline and 10 per cent glucose (50 per cent each)
      10 per cent glucose
   b. Intraperitoneally
      Physiologic saline
   c. Intravenously
      Physiologic saline
      Glucose solution
      Whole blood
      Serum

4. Food similar to that for mild cases, but with slower increase. May have to give by gavage for several days or even longer. Little gained by too much foreing of food during first week of illness. This is time to force glucose solution and fluids, with foods of secondary importance.

5. Very slow and gradual return to normal diet, with attempts to prevent relapses which tend to be common due to prolonged intestinal sensitivity.

6. Oleum percomorphum, ascorbic acid, and thiamin chloride definitely indicated throughout. Do not use fruit juices, orange juice, cereal waters, etc.

The early administration of blood transfusions has saved many an infant's life, not only in the severe bacillary dysentery infections, but also in those sicknesses previously referred to as acute intestinal intoxications. However, one must find some dividing line for these cases. In former years, I used blood transfusions frequently, often repeatedly, and quite early. However, I found also that, with the early use of glucose solution orally and intravenously and of saline intravenously, subcutaneously, and even intraperitoneally, it was not nearly so necessary to resort to transfusions as an early procedure. Glucose, 10 per cent solution, by mouth is well tolerated in even the most severely ill dysentery patients, and an increase in the diarrhea does not occur as a result of its use.

It is always important to establish, temporarily at least, an improved blood volume. This can be done by giving glucose in saline intravenously just prior to the transfusion. Some instances of an unfavorable response have been reported in cases in which fluid therapy did not immediately precede the blood transfusion.

In the well-nourished patients, one certainly ought not to have to resort to transfusion nearly so early as in thin, poorly nourished youngsters. It is likewise in these thin, poorly nourished, or even marantic youngsters that serum transfusions may work better than blood transfusions.

I can summarize my own feelings in the matter best by saying that, although blood transfusions are extremely important in many of these cases, it has become progressively less necessary to resort to blood transfusion if the patients are seen early and are properly managed otherwise from the standpoint of early administration of saline and glucose, with judicious administration of food, preferably cultured lactic acid milk to which gelatin and even glucose may be added at times with benefit.

Now, when one sees a relatively advanced case in which the patient is in an extremely toxic state and the dehydration is severe, there is no doubt but that blood transfusion should be given and repeated as often as necessary, because in these cases it certainly accomplishes things which glucose and saline alone will not. I do not resort to blood transfusion then unless the patient (1) is extremely poorly nourished; (2) is very dehydrated and toxic and fails to respond quickly to glucose and saline administered intravenously and otherwise, in which case I use the transfusion early; or (3) otherwise presents such obvious symptoms of intoxication that I would regard him as a severely ill infant.

DR. E. C. MITCHELL, MEMPHIS, TENN.—I would like to emphasize the importance of the use of rest in the management of infections of the intestinal tract. Food should be withheld in such a manner as to provide this rest. I prefer 5 per cent glucose in Ringer's solution and have been getting splendid results with it in the form of a continuous intravenous drip. Where it is possible to employ the intravenous drip, one can frequently avoid extreme states. As far as drugs are concerned, I give opium in some cases and feel that it has a definite place. Several years ago, after talking with Dr. Ivy about the use of sodium thiocyanate on dogs, I was stimulated to the point of using it experimentally in bacillary dysentery infections. One gram was apparently not toxic to adults. In the last five years, I have used it frequently. It has been particularly successful in the Shiga infections, if given early; it should be given in the first twenty-four hours. I give 20 mg. per kilogram, and this I give intravenously in the really toxic cases. If the infection has not really gotten under way, ⅓ grain per kilogram will help to prevent the disease.

DR. MATTHEW WINTERS, INDIANAPOLIS.—Dr. Tompkins and I have been interested in the use of a pectin agar preparation for the treatment of diarrhea of infants. Dr. Tompkins has reported an experience with apple therapy in the treatment of diarrhea of infants. There were several objections to its use: (1) apples were scarce in the diarrhea season; (2) they were relatively high in cost; and (3) the nursing care involved was excessive when several infants were being fed the apple diet. With this in mind, we interested ourselves in an attempt to find a substitute. In the beginning we used 175 Gm. of dextrimaltose, 6 Gm. of pectin, and 8 Gm. of agar-agar. The substances are mixed together dry. The end product is not noticeably hydroscopic and will keep indefinitely. The cost is low. The formula contains about three times as much pectin as a corresponding amount of the apple preparation. The milk or water is boiled with this mixture over an open flame for from three to five minutes and is then poured into cups. This generally constitutes one day's feeding on the basis of a three-hour schedule. The preparation made with the whole milk is a highly concentrated food, as each feeding is two or three tablespoonfuls. If fat is not desired, skimmed milk may be used. Various flavors may be used, such as vanilla, chocolate, or fruit. Although they are not needed for infants, flavors may be desirable for small children. The feeding can be made concentrated by using powdered milk and decreasing the amount of liquid. The studies were controlled by cultural and other suitable methods. In an original series of forty-two infants, twenty-four were fed pectin agar mixture and eighteen were fed raw apple as a control. Time does not permit a full discussion of the observations here, but the patients responded in much less than the average time; the stools were liquid for only 1.3 days on an average, as compared to stools liquid for an average of 4.1 days for those on the apple diet. The average time of transition to a normal diet was shorter and required less caution, and the patients in this group showed an average gain in weight of 50 Gm. per day, while the group given the apple diet lost an average of 70 Gm. per day. Ten patients had Flexner dysentery and five had Sonne dysentery bacilli. These responded more slowly as a whole.

The last word has not been written on therapy for infantile diarrhea, but this pectin agar feeding would certainly seem to promise additional help in cases of this condition. Certainly its ability to control diarrhea and promote gain in weight simultaneously is not to be minimized. The simplicity of the procedure and its efficacy in our experience would seem to recommend its use.

CHAIRMAN LYON.—A question about the agglutinins in patients with bacillary dysentery. When do they appear? I have already said that in the newborn infant they appear slowly or not at all. In the Shiga and Flexner types in infants and

older persons, they appear fairly quickly, usually in from five to seven days, whereas in the Sonne type the agglutinins come up more slowly and would seem to be less intense, indicating a less intense and perhaps even a somewhat less specific antigenicity.

Infections are really not strikingly common when one considers the high incidence of the disease. However, they do occur, and one of my own children had an infection at 15 months of age and again at 12 years, both times a Flexner strain. She has no agglutinins now, four years after her last attack.

DR. J. W. BRITTON, ANNISTON, ALA.—We see a great deal of this condition in Alabama and call it colitis. I have used sulfanilamide with it, with excellent results.

CHAIRMAN LYON.—I have heard of other instances where sulfanilamide has given good results in cases of "bloody diarrhea." However, Dr. W. B. Hunter of Huntington, in a series of cases, was able to find any continued good results, although he was of the impression that he got strikingly good results in the first few cases so treated. He has given up this treatment for the present.

DR. C. O. TERRELL, FORT WORTH.—Do you have trouble getting cultures from the stools? Do you take the culture from the rectum or from the stools? What media do you use?

CHAIRMAN LYON.—Generally, in the summer, if one gets the freshly passed stool, one can take the culture directly from a small collection of the bloody streaked pus, rather than directly from the bowel. It is quite important to keep the stool from drying up, and the percentage of positive cultures falls off very rapidly as time elapses after the stool is passed from the infant. I have usually used Teague medium. One reason I believe cultures are difficult to get is that there are so many of us who are not expert enough in bacteriology nor persistent enough in nature. I feel quite certain that is why there has been such a difficulty in the past in getting positive stool cultures.

DR. COOPER.—In our recent bacteriologic study of infants and children with acute diarrhea, we found sodium desoxycholate citrate medium to be the best for the detection of *Shigella paradysenteriae* in the stools of such patients. This medium inhibits the growth of most strains of *Escherichia coli* and gram-positive microorganisms. With this medium we found that culturing two stools gave almost as high a percentage of positives as were found when five stools were cultured on this or three other media. These media may be listed as follows, in the order of their efficiency, beginning with the best: sodium desoxycholate citrate, MacConkey's, eosin methylene blue, and Endo's. The latter medium is widely used in hospital laboratories, and its failure to detect members of the *Shigella* group may easily permit discharge from the hospital of patients who are still harboring these bacteria in stools, thus increasing the hazard from carriers.

It has been our experience that the Sonne type of *Shigella paradysenteriae* is not readily identified unless the lactose cultures are observed for a period of from three to six weeks, because many of these cultures are slow lactose fermenters.

DR. HOYER.—We have been particularly interested in the diarrhea and dysentery problem in Cincinnati during the past five years.

A study of the mortality rates showed that most deaths from diarrhea occur in children under 2 years of age, during the summer months, and in the congested districts.

In the summers of 1934 and 1935, we carried on a study in a congested area of the city in an effort to determine the cause of diarrhea, and if possible, to lower the mortality rate. The study was similar in some respects to the one carried out in Richmond a number of years ago. Nurses made regular weekly visits to the homes in which there were children under 2 years of age. The mothers were instructed to report immediately any change in the character or frequency of bowel movements. When a case was reported, daily visits were made to the home. A number of details were studied, such as refrigeration, screening, and sanitation; several factors in the cause of diarrhea were substantiated, among which was the fact that in 51 per cent of the cases of diarrhea the problem of food was involved, and in approximately 33⅓ per cent there was an upper respiratory infection. In the light of the work done at the Children's Hospital last year in which it was shown that 40 per cent of the diarrhea is really dysentery, I am inclined to believe that a large part of the 51 per cent may have been due to contaminated food, rather than spoiled food or indiscretions in diet.

Diarrhea in patients under 2 years of age and bacillary dysentery are reportable diseases in Ohio.

The past two summers, from May 1 to November 1, we have had a nurse at the Board of Health call each hospital every morning for the list of the cases of diarrhea admitted and discharged. Likewise, the Babies Milk Fund and other nursing organizations have reported their cases. Physicians have been encouraged through the Academy of Medicine to report their cases, but as yet without much success. The cases discharged from the hospital were visited at home, by a nurse, in an effort to prevent recurrences.

There were approximately 1,500 cases in 1937, and in the past summer, approximately 1,200 cases. There were approximately 200 instances in which there was more than one case in the same house, but not necessarily in the same family, and 70 some odd instances where there was a recurrence. This brings up the important question of carriers, if we are to assume that from 40 to 50 per cent of the cases of diarrhea are really a bacillary dysentery.

Dr. Lyon's graph explains in part our mortality rate this year. We were feeling rather elated about it until September. There had been but nine deaths, in patients under 2 years of age, reported in the city from May 1 until September 1, which is quite a reduction. Then September came, and there were eight deaths.

The spring and early summer were quite wet, and then we had quite a long dry spell beginning the middle of August and extending through September. This would make a graph similar to the one drawn by Dr. Lyon, showing the mortality rate in those countries where there is excessive rainfall in the early summer and drought in the late summer.

CHAIRMAN LYON.—Dr. Hoyer's remarks on the mortality rate are interesting because our experience in Huntington this summer is similar to what he reports for Cincinnati.

DR. CASPARIS.—We should get more units of vitamins A, B complex, C, and D into the patient during diarrheal states than otherwise. Fortunately, oleum percomorphum and similar A and D concentrates can be given orally in dosages that are tolerable, and the thiamin chloride, nicotinic acid, and ascorbic acid tablets can be given dissolved in the milk.

CHAIRMAN LYON.—I recommend using the vitamins referred to in the diarrheal states and taking a chance on their absorption. I have seen scurvy, sore tongue, and stomatitis develop not infrequently in the past when we had to deal with poorly nourished children who were on protein milk for a long time.

NINTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

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Round Table Discussion on Common Skin Diseases in Children

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Secretaries: Byron K. Rust, M.D., Indianapolis, Ind.
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CHAIRMAN JAMIESON.—The dermatoses selected for discussion as those most frequently encountered are: various forms of pyoderma, including impetigo contagiosa, ecthyma, furuncles, and impetigo neonatorum; fungous infections, both ringworm and *Monilia;* alopecia areata, nevi, dermatitis venenata, psoriasis, pityriasis rosea, warts, vaccinia, urticaria, molluscum contagiosum, and dermatitis medicamentosa. A request was made that eczema not be included in this presentation.

The clinical features and diagnostic criteria of **impetigo contagiosa** are shown in the first group of slides. The early vesiculation which may be small or large in extent is always superficial, ruptures early, and is followed by an exudation of yellowish, seropurulent fluid which soon dries into a characteristic crust. This crust is elevated above the skin level, is not firmly attached, and appears to be stuck on the surface. On removal a moist surface covered with exudate is seen.

The lesions vary in number from one to many, the longer the duration of the disease, the greater the number. As the disease is most commonly encountered on or about the face, however, the greatest number of lesions is usually observed there. Other areas may be involved also, especially on the hands, arms, legs, and buttocks, or anywhere the child might be able to reach. In some of the older children or in those who may have a low bacterial resistance, ecthymatous lesions may follow various forms of infections and are found chiefly on the lower extremities.

Furunculosis may be a concomitant complication of various forms of pyoderma, or it may be a sequel, or it may be entirely independent of the other forms. The symptomatology of this condition is too easily recognized to require elaboration.

Impetigo may be confused at times with tinea circinata if the lesions have healed in the center, leaving an active border, but it should be remembered that tinea circinata is a much slower process. It begins as a small, reddened, scaly lesion with slight elevation, spreads centrifugally, and produces a small annular lesion without exudation or the seropurulent crusting that is so characteristic of impetigo. It also is usually single, but may be multiple.

At the oral commissures herpes simplex and impetigo may be mistaken, although the usually single lesion of herpes is composed of a group of small deep vesicles accompanied by a stinging sensation, some sensitivity on pressure, slight swelling, and no tendency to crusting in the early stages.

Impetigo neonatorum, often referred to as pemphigus neonatorum, produces the same type of lesion in the newborn infant as does impetigo in older children. It may become serious or even fatal if a large portion of the body surface is involved. The question of whether a single seropurulent vesicle is a true impetigo or merely a follicular pustule may be difficult to answer, but all lesions of this type in the newborn infant should be treated as potentially impetiginous.

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Treatment of the usual form of impetigo involves no difficulties, for a mild antiseptic (boric acid or potassium permanganate) solution to soak off the crusts, followed by an antiseptic ointment (ammoniated mercury, 2 to 5 per cent), is usually sufficient to effect a cure in from ten to fourteen days, observing, of course, the usual procedures of sterilization of hands, towels, clothing, etc.

More resistant cases may require in addition the use of bacterial vaccines, ultraviolet radiation, silver nitrate, metaphen, merthiolate, or a host of others too numerous to mention.

Owing to the rapidity of spread of impetigo neonatorum, isolation precautions should be taken; the nurse should be carefully instructed in using surgical asepsis in all care of lesions, sterilization of all clothing, furniture, rooms, etc., in order to limit the spread. Ultraviolet radiation may be employed also over the entire body surface.

It is still a moot question, with regard to the prevention of impetigo neonatorum, whether or not to bathe the newborn infant. Some institutions use one method, and some use another, with apparently equal results.

Too much bathing can render the skin more vulnerable to infection, and bathing therefore should be restricted to a minimum for cleansing and should be followed by oil rubs or the use of a mild mercurial ointment; one should be on guard, however, for mercurial intoxication.

Calomel in the dusting powder may be used also, or a 1:10,000 bichloride dip for the infant may be quite satisfactory. Sterilization and rupture of individual lesions, followed by painting with 10 per cent silver nitrate, should be done with all new small lesions of the vesiculopustular type, as these are all potentially infectious.

The subject of **fungous infections** in children is a large one and includes all forms of ringworm infections from the head to the feet as well as *Monilia* infections producing thrush, perlèche, and eczematoid dermatitis of the diaper region.

Tinea circinata (corporis) requires little attention, as it never produces lesions or symptoms of any consequence. Usually appearing on the face, neck, or arms, its onset is a small, reddish slightly scaly lesion which slowly enlarges to produce an annular lesion of from 1 to 3 cm. in diameter, with a clear center. These lesions may be single or multiple and are occasionally mistaken for impetigo (q.v.), psoriasis, annular syphilide, or pityriasis rosea.

The history will usually reveal infected playmates or an infected cat or dog as the source of the condition. Microscopic examination of the scales is sufficient to differentiate easily tinea circinata from the other conditions mentioned. Local treatment with mercury, iodine, or almost any efficient parasiticide is followed by a speedy cure.

A much more serious condition is encountered when the scalp becomes infected with the *Microsporon audouini* or *M. lanosum*. The fungus here invades the hair follicle and hair shaft, the removal of which is necessary to establish a cure. Transmission of this infection is likewise due to contact with other infected children, cats, or dogs, or the use of infected brushes or caps.

Onset may be rather insidious, for some varieties develop as a grayish, scaly patch on the scalp, followed later by alopecia, either partial or complete. Some fungi attack the hair, produce little or no scale, and cause the hair to break off, giving the appearance of black dots. Still others produce a complete alopecia in the affected areas, the so-called "bald ringworm."

Development of the patches usually is not very rapid; they may be small or large and vary from one to a large number scattered over the scalp. Subjective symptoms are negligible unless a secondary pyogenic invasion occurs, with the production of a kerion.

It is usually unnecessary in the average mild case to make an identification of the organism, but in stubborn or severe cases it is often advantageous to know whether one is dealing with a large-spored or small-spored organism of either the ectothrix or endothrix variety. This can be determined readily by soaking the hair in 10 per cent sodium hydrate solution and examining it with the microscope.

For rapid and efficient diagnosis in differentiating tinea capitis from alopecia areata, syphilis, etc., the hair may be examined by means of Wood's filter. This is a nickel oxide glass attached to a water-cooled ultraviolet lamp. The examination is made in a dark room, and it is very striking to see the fluorescence from the affected hairs by means of this filtered ultraviolet ray. It should be remembered, however, that the large-spored fungus does not cause fluorescence.

The entire scalp can be examined easily in a few minutes for diagnostic purposes, and on subsequent visits the method may be used to detect stray infected hairs that might cause recurrences. In certain instances, the dog or cat at home may be examined in order to discover the primary source.

Treatment of tinea capitis, to be effective, must be carried out thoroughly and continued for some time after apparent cure.

It may be unnecessary to clip the hair in dealing with small single patches, but if there are many infected areas, treatment is greatly facilitated and cure is hastened by keeping the hair short. Washing with tincture of green soap, followed by the application of ammoniated mercury or dilute tincture of iodine, may be all that is necessary to effect a cure, but one should persist in the treatment until all the broken stumps of hairs have disappeared. Care should be used also in the application of these drugs that a severe dermatitis is not produced. In these applications, ointments or oils may be used as vehicles, those with the greatest power of penetrating the hair follicle being the most effective, but in case of doubt as to the proper strength of the application, begin with weak preparations and increase later if necessary.

In the event the infection is severe, widespread, or has developed a kerion, an epilating dose of x-ray radiation may be necessary, using the technique and dosage according to MacKee's method. If proper dosage is used, the hair should fall out in about two to three weeks, with regrowth in two or three months. Local applications should be continued until all affected hairs have disappeared as shown by examination with Wood's filter.

In schools or other institutions where tinea capitis is a serious problem, x-ray epilation may be used or thallium acetate employed. As the use of this drug is not without danger, one should be thoroughly conversant with its use before employing it. Toxic and fatal results have been reported even though the ratio of dosage to weight (7 to 8 mg. per kilogram) had been adhered to. After its use, the hair should fall out in approximately two to three weeks.

Tinea cruris, "jock strap itch," the eczema marginatum of the older writers, is found occasionally in children either with or without ringworm of the hands and feet.

This condition is eczematoid in character, erythematous, slightly scaly, with a sharply demarcated border in a festoon shape on the inner aspect of the upper thigh. One or both sides may be affected; the pruritus is often severe and recurrences are frequent.

Local applications of potassium permanaganate, 2 per cent ammoniated mercury, crude coal tar, etc., may be used, care being exercised to avoid irritation on account of the sensitivity of the areas involved. Fractional (75r.) doses of x-ray radiation may be employed in refractory cases, with the proper precaution in protecting unaffected areas.

Epidermophytosis, eczematoid dermatitis of fungous origin, of the hands and feet presents at times a serious problem in children. The symptomatology is too

well known to require repetition here, except to say that the usual symptoms are eczematoid in character, with erythema, pruritus, vesiculation, scaling, and peeling, and may be found on the palms and fingers, soles, and under and between the toes, especially in the last two. The course is variable and recurrent, as in adults. Diagnosis is confirmed by microscopic examination of the scales or vesicle tops. This, however, is not always necessary, and in many instances of clinically undoubted fungous infection, the fungi are not found with the microscope.

Treatment consists of soothing astringent and antiseptic applications in the acute cases, using boric acid, Burow's solution, or potassium permanganate, with half-strength Whitfield ointment after the acute symptoms have subsided. Tar or ichthyol may be substituted in those patients with sensitive skins. Ultraviolet radiation and small doses of x-ray radiation are often of value. Prophylactic measures should include sterilization of stockings and shoes, as well as prohibition of contact of the unprotected feet with the floor or ground.

In chronic and recurrent cases trichophytin may be employed although the results so far reported have been variable. Iontophoresis with copper sulfate gives promise of being a useful adjunct in resistant cases.

Varying forms of dermatitis from infection with differing types of *Monilia* are encountered in children, one of the most common being thrush, as seen on the mucous membranes. This does not often cause much trouble as it is usually removed readily by mild antiseptics or boric acid solutions.

Other types of *Monilia* infections may appear as intertriginous dermatitis or as reddish, superficial, slightly scaly, sharply demarcated, eczematoid patches in the diaper region. These are rarely serious, for the lesions soon involute following the use of mild parasiticides, and prevention of contact and irritation, as well as removal of the source of infection.

Boric acid, potassium permanganate, ammoniated mercury, and gentian violet are all valuable in the different forms of moniliasis. Baths of hyposulfite of soda can be used in extensive cases as this is nonirritating, nontoxic and mildly fungicidal. In small resistant areas a 1 per cent chrysarobin ointment is often of value.

A very distressing condition for the parents as well as the child is a well-developed alopecia areata. Appearing as it usually does after the fifth year, its initial lesion is a rapid loss of hair in one or more patches which soon become bald and perfectly smooth, with the surrounding hair easily removed by slight traction. The disease may remain limited to one patch, but it is commonly found in multiple patches, even to the extent of involving the entire scalp as well as the eyebrows and eyelashes.

In the areas involved there is no evidence of any infection or inflammatory disease, but at times there is some confusion in differentiating alopecia areata from tinea capitis and syphilitic alopecia. As the latter is a manifestation of acquired secondary syphilis, it need only be mentioned here.

The diagnosis between alopecia areata and tinea capitis can be easily and rapidly made by means of the above-mentioned Wood filter by means of which fungus-infected hair will fluoresce in a dark room. However, the rapidity of onset, loose peripheral hair, lack of erythema, and rapid spread will usually serve to make a correct diagnosis.

If the treatment were as easy as the diagnosis, alopecia areata would be a satisfactory disease to treat, but as very little is known of the etiology, treatment must be symptomatic. Fortunately, spontaneous recovery is the rule, except in a few unusually protracted cases or in those with universal alopecia. It appears to be on a toxic or trophoneurotic basis and would, therefore, indicate a thorough investigation of tonsils, teeth, ears, and the endocrine system in a search for any abnormality which could be held responsible for some functional nerve disturbance.

In addition to correcting any abnormality found, local stimulation in some form is advisable and often appears to hasten the regrowth of hair. Applications of iodine, phenol neutralized by alcohol, ultraviolet radiation and high frequency current may be used with varying success, but it is often surprising how frequently results are obtained by long continuation of any or all of these methods. Endocrine therapy, unless definitely indicated, should be employed with caution.

Nevi of all types are encountered in children and may vary from the small, brownish, flat or slightly elevated mole to the large, deep bluish-red, cavernous hemangioma. I am glad to have received a positive and definite answer to a question I have long wanted to ask the pediatricians regarding spontaneous involution of certain types of vascular nevi. As the pediatrician follows the child for years, he has an exceptional opportunity to observe the behavior of these untreated vascular nevi, and I am happy to be able to tell the mothers of some of these children afflicted with nevi that some nevi will disappear spontaneously.

It is difficult to come to a definite decision regarding the safety of removing the brownish, slightly elevated nevi so commonly seen. It seems to me that no patient should be urged to have these removed unless some pathologic change is occurring or the lesion is in a location where it will be irritated easily and frequently. If removal is decided upon, any method which will remove it completely without prolonged irritation will be satisfactory—surgery, electrodesiccation, cutting current, etc. In a few cases in which superficial, dark-brown nevi involved a fairly large area of the face and in which the size and location precluded the use of surgery or electrodesiccation, excellent results were obtained by freezing with the solid carbon dioxide stick.

Hemangiomatous nevi present a different and often difficult problem, for so many are situated on the face and the child's parents insist upon treatment. In the majority of cases early treatment is productive of better results and shorter treatment is acquired. We have seen with chagrin a few patients who were counselled to delay treatment, only to see the nevus become much larger and deeper during the waiting period.

In the treatment of the small nevus araneus and the larger slightly elevated vascular nevus—the "strawberry nevus"—the solid carbon dioxide stick is extremely valuable, often removing the lesion with one or two applications and leaving a minimum of scarring, and often none at all.

Electrodesiccation under local anesthesia will be found valuable in some small lesions in older children, but a certain amount of scarring is to be expected.

A method which I believe will grow rapidly in favor is the use of sclerosing agents in lesions not suitable for radium or x-ray therapy. Those who have tried this method, which consists of injection at two- to four-week intervals of minute quantities of the fluid (diluted quinine urethane) into various parts of the nevus, are quite enthusiastic over the results. It would be advisable, however, to familiarize oneself in its use by beginning on nevi of the body in the event of an unexpected, disconcerting slough. This method is now receiving preference over radium in lesions about the eyes. With perfected technique, the sclerosing method may eventually supplant the use of radium in most cases.

Radium seems to me to have an uncanny, selective action in the treatment of cavernous hemangiomas, and many of these large, disfiguring nevi gradually melt away, often disappearing without leaving a trace.

It is my belief that radium is most effective if used in small doses at two- to three-month intervals and applied well filtered and no closer to the skin than 1 cm. One year or more may be required for complete cure, but patience in treatment is a necessity here; forcing the treatment might easily lead to overdosage. Even

as small an amount as 10 mg. of radium properly used is capable of producing results that are almost miraculous. This is especially true in small lesions that are too deep to be treated successfully by freezing.

In the consideration of contact **dermatitis** in children, we must inevitably come into conflict with the condition classified as eczema, which does not enter into this round table discussion.

The symptoms of contact dermatitis (venenata) are essentially those of eczema; i.e., erythema, pruritus, edema, vesiculation, bullae, exudation, etc., all in varying degrees depending upon the sensitivity of the child's skin, the duration of the contact, and the activity of the sensitizing agent.

As in the adult type, the affected areas are more or less limited to the parts exposed to the irritant, such exposure varying from once to many times before the development of the dermatitis. The symptomatology is the same in all cases, due allowance being made for the individual sensitivity, frequency of contact, and the type of irritant.

It is not difficult as a rule to diagnose dermatitis venenata (contact), but the greatest difficulty is often encountered in discovering its source, removing it and thereby promptly relieving the condition.

After determining that the dermatitis is from external sources, consideration should be given to the location, as that may clearly indicate the most probable offender. It may be necessary to make a prolonged study of these cases; observation of home environment may even be required before the agent or agents can be found. The intelligent cooperation of the parents is also invaluable if they can be made to appreciate the many obstacles in the search and the potentialities of everything coming in contact with the child's skin.

While the sources of contact dermatitis are innumerable, the substances most frequently incriminated include clothing, especially fur and wool, soap (too strong or too much), powders, toilet waters and perfumes, washing solutions or powders used on clothing, flowers, plants and pollens of all types, paint (toilet-seat dermatitis), animals, rugs, draperies, upholstery, cosmetics used by mothers, floor cleaners (creeping babies), house dust, insecticides—an endless list.

Best results in treatment are obtained by the one who is the best detective. If the irritant is discovered and removed, the required treatment is merely protection of the affected parts and the application of bland and soothing lotions or ointments.

If the cause is not removed, exacerbations will occur with repeated contacts and the result will be a very discouraging failure. Miraculous cures, however, are obtained often by proper recognition of the condition, with discovery and removal of the source.

Psoriasis is encountered frequently enough to include it in this group. Although it is uncommon before the age of 5 years, it has been reported in infants 6 months of age.

As the pediatrician is far more likely than the dermatologist to observe the onset of psoriasis, he may encounter patients with only a few small, scattered lesions or a generalized acute eruption.

Either type may present difficulties in diagnosis, but in these children we frequently find some familial history which is suggestive. There is also an absence of definite pruritus, frequently an involvement of the common sites of predilection (elbows, knees, and scalp), seasonal recurrence, and in all lesions, even the earliest, a fine pearly-white scale under which is seen a minute hemorrhagic punctum after removal of the scale. The nails may also show some dystrophy in chronic cases.

These eruptions vary from a few small scattered lesions to large and extensive patches, and, as in adults, the prognosis is dubious and variable regarding amelioration and cure. Restricted diet is a factor in treatment in a certain few cases, but its efficacy is uncertain and questionable.

Fecal infections should be removed, and any other abnormality corrected. A balanced diet with proper vitamin content should be given, together with the use of the usual local treatments of colloid baths, ointments with salicylic acid, tar, ammoniated mercury, chrysarobin, and anthralin. Autohemotherapy, salicin given orally or intravenously, and ultraviolet radiation all prove efficacious at times, as do arsenic in one form or another and x-ray radiation. The two last therapeutic measures should be used sparingly in children and should be watched carefully, for either one is capable of producing serious late results if used injudiciously.

An eruption encountered fairly often in children is pityriasis rosea, frequently confused with other dermatoses. Although the dermatologists have encountered many atypical eruptions of pityriasis rosea in the past few months, I do not recall seeing these atypical forms in children.

The usual history is obtained of the development of the herald patch followed in a few days or a week, by eruption on the trunk, arms, and legs. Although the clinical appearance of the herald patch and secondary lesions is quite characteristic, this condition is often diagnosed as secondary syphilis, dermatitis medicamentosa, erythema multiforme, or tinea circinata. The course of the disease from the onset of the herald patch is usually sufficient to make the diagnosis, but a few cases, in which the exanthem is chiefly maculopapular, could be mistaken for syphilis. These lesions, however, are very pruritic and are most abundant on the trunk; some are elongated and follow the cleavage lines of the skin. The Wassermann reaction in pityriasis rosea is also negative.

Differential diagnosis from dermatitis medicamentosa in some cases may be made with certainty only by an exclusion and by omission of all medication.

The multiform character of the deep red lesions of erythema multiforme, the location on the neck and extremities chiefly, the rapid onset and course, together with frequent systemic manifestations, should serve to make distinction from pityriasis rosea comparatively easy.

The disease most frequently confused with pityriasis rosea, however, is tinea corporis, the circinate character of many lesions giving the impression of a fungous infection.

The multiplicity, the location on the trunk chiefly, the size, the oval rather than round shape, involution, and the course of pityriasis rosea should make differentiation easy. It is sometimes necessary, however, to examine scrapings from the lesion when only one circinate lesion is present as this might be the single herald patch of pityriasis rosea or tinea circinata although the clinical characteristics and subsequent development of the two lesions are quite different.

Very little treatment is required in pityriasis rosea because the disease terminates spontaneously in from one to two months. Recurrence is rare.

Warts of all shapes, sizes, and types are often observed in children of all ages. They may be single, few, or many, and may be located anywhere from the head to the feet.

Verruca plana juvenilis, verruca vulgaris, and verruca plantaris are too well known to require description or differentiation, although the plantar type is often overlooked as it is frequently surrounded and covered by a callus of secondary development.

Every possible form of treatment has been used for the flat and verrucous types, with equally variable success, the gamut including magic, mental sugges-

tion, magnesium sulfate in very small doses, arsenic, mercury internally, and bismuth intramuscularly. Locally may be used salicylic acid, resorcin, acetic acid, trichloracetic acid, nitric acid, solid carbon dioxide stick, fulguration, electrolysis, radium, and x-ray.

The mode and extent of application of these agents will necessarily vary with the number, type, and location of the lesions to be removed, the more drastic measures being employed in single lesions where the risk of scarring can be disregarded. They all have a place in the treatment of warts and in some instances they may all be used with greater or less success; in other instances, recurrences follow any method of removal followed by spontaneous disappearance of the warts at some future time.

The plantar wart, however, on account of its location, is usually painful and may be followed by a foot deformity if allowed to go untreated.

In these cases, softening with salicylic acid plaster followed by x-ray radiation fulguration or curettage with local anesthesia is successful if persisted in. The latter method is often the method of choice because it is rapid and one treatment is usually sufficient. The one objection to its use is that walking is usually impossible for a few days. Fulguration would offer the same objection, and recurrences are as frequent after fulguration or excision as after treatment with any other method.

X-ray and radium if carefully used, limiting the action to the actual lesion, will give good results in the majority of cases, but it is usually necessary to employ salicylic acid plaster in addition to radiotherapy.

In reply to a request for a few words on **scabies**, it might be said that typical scabies is diagnosed easily when one remembers that the lesions usually begin around the wrists in children or in the interdigital webs and then invade other areas that can be reached easily. The center of the back commonly is not affected. The arms, thighs, the buttocks especially, and the trunk are involved, presenting early lesions of small, hemorrhagic, punctate excoriations, together with eczematoid and often pyodermic evidence of trauma and secondary staphylococcic invasion. Primary papulovesicles may be found and also burrows on close examination, but it is unnecessary to find the burrows in order to make the diagnosis. Pruritus is always present and is more severe when the child is in bed or is warm. Others in the family may be affected as well as playmates of the infected child.

A few days of proper treatment should suffice to cure the average case of scabies, but prolonged pruritus and dermatitis may be the result of the use of too much sulfur or other parasiticide. This may be avoided by the use of an oil rub every morning, application of the parasiticide for only three days at a time, and then the use of oil rubs twice a day in the intervals.

Sulfur alone or in various combinations is usually sufficient for a cure, accompanied by the usual hot bath and complete repeated sterilization of all clothing in contact with the skin.

Many and varied types of erythematous and vesiculated eruptions may follow **vaccination.**

The exanthem may be sparse, limited in extent, or it may be profuse and generalized. Many that have been seen recently and shown on the screen today bear a marked resemblance to erythema multiforme in its varied manifestations. In all cases, however, the history of preceding vaccination and the presence of an active inoculation will enable one to make the correct diagnosis. Spontaneous involution occurs as the local vaccination reaction subsides.

Allergic manifestations of **urticaria** are encountered at times, with the usual small or large, few or many urticarial wheals on any or all parts of the body. Diagnosis is easily established, but it is not without a great deal of difficulty at times that the sensitizing agent is discovered.

While a large percentage of urticarias are of food origin, it should not be forgotten that in children a number of external agents are capable of producing urticarial lesions which may be localized or widespread. These agents include various forms of plants, clothing, insects, heat or cold, parasites, neurocirculatory instability, foreign proteins, etc. In these cases discovery and removal of the irritating agent produce a prompt recovery.

If a food is the agent, it may require a considerable search to discover the right one; in general, however, if free catharsis is employed, restriction of diet to those foods which are usually considered nonallergic is soon followed by recovery. Alkalinization, the external use of antipruritics, and adrenalin or ephedrine in severe cases may be employed.

A persistent type in which the lesions take on a prurigo-like appearance is referred to by the English as lichen urticatus. The lesions here are papular; they are worse in the summer, and appear more often on the trunk. They are very resistant to all treatment. This form is often referred to as a papular eczema.

Difficulty is often experienced in differentiating molluscum contagiosum from verrucae. In my experience, this condition is observed much more frequently than in former years, although it causes very little actual annoyance subjectively or objectively. The lesions may be single or numerous, appearing with slow development on the face, neck, trunk, or extremities as discrete papular lesions which are usually noninflammatory, and presenting a central crater-like opening, which is lacking in the flat and verrucous warts. Through this opening can be expressed a central plug composed of hyalinized and dystrophic epithelial cells, the molluscum body.

The condition is mildly contagious, and as its development is so slow, the entire body surface should be inspected at intervals in order to prevent the development of new lesions, or at least to destroy them in their incipiency.

Expression of the central plug, followed by local cautery with phenol or iodine, is sufficient to destroy the individual lesions, but care should be exercised to prevent the development of new lesions or transmission to others.

In these days of intensive vitamin, endocrine, and medicinal therapeutics, it may happen that some otherwise obscure **exanthems** can possibly be explained on the basis of medication, and it is well to remember that many drugs are capable of producing eruptions of various types and varying degrees.

The chief offenders are the halogens, bromides, and iodides, which may cause lesions varying from mild acneform papules or pustules to nodular, vegetative, or bullous lesions.

Phenolphthalein is so widely used now that one must bear in mind the possibility of its use resulting in many forms of toxic lesions, some of the erythema multiforme type, and some of erythematous plaques which leave violaceous pigmentation of the fixed eruption type.

Belladonna and quinine can produce scarlatiniform exanthems, the latter sometimes causing minute vesiculation of the hands and feet resembling pompholyx or ringworm.

Arsenic also should receive a prominent place as a dermatitis-producing drug, because many persons have taken arsenic for long periods, with resulting pigmentation of the body or keratoses of the palms and soles; others have had toxic erythemas which have progressed to exfoliative dermatitis (arsphenamine type).

DISCUSSION

DR. R. N. ANDREWS, MANKATO, MINN.—What is the value in the use of vaccines in prolonged cases of impetigo which do not seem to respond to the usual routine treatments?

CHAIRMAN JAMIESON.—The judicious use of vaccine is of great value in some cases. It is advisable to identify the organisms involved and is usually more effective if autogenous vaccines are prepared. Stock vaccines may be used in such a way that the patient's resistance to the infection is not lowered because of administration of too frequent or too large a dose. The greatest danger from this form of therapy lies in overdosage. Watch your patient carefully for signs of decreased resistance.

DR. L. S. ROBINS, CHICAGO.—Has sulfapyridine been used in the more resistant cases of pyodermia?

CHAIRMAN JAMIESON.—Not to my knowledge. I would be inclined to stay away from these more drastic drugs in treating a condition which is not so serious as the results from the drug might be.

DR. J. M. ULRICH, AKRON, OHIO.—What about the use of gentian violet in impetigo?

CHAIRMAN JAMIESON.—A great deal would depend upon the site of the lesion. You certainly would not use gentian violet on the face of a young girl. If the treatment could be used at home, gentian violet would be a useful adjunct in the treatment. The same may be said for silver nitrate.

DR. E. S. WATSON, ELMHURST, ILL.—Is it true that impetigo does not respond as well to ammoniated mercury now as it did previously?

CHAIRMAN JAMIESON.—I have not had that experience, but you may be dealing with different strains of staphylococci or streptococci. You may have to vary the treatment from time to time. This may be due to change of organisms or to individual resistance.

DR. R. P. ROGERS, GREENWICH, CONN.—What do you advise for the treatment of impetigo superimposed upon the venenata infestations?

CHAIRMAN JAMIESON.—Use mild antiseptics, Burow's solution, potassium permanganate, and ultraviolet light.

DR. R. A. CRAIG, KOKOMO, IND.—Lots of large blisters resembling pemphigus spread under an ointment, but they are checked with gentian violet.

CHAIRMAN JAMIESON.—You are probably thinking of a pemphigus neonatorum. The lesions frequently spread with the use of an ointment which seems to seal the lesions, allowing the organisms to continue active growth without hindrance.

DR. A. C. GIPSON, GADSDEN, ALA.—What do you advise in the treatment of impetigo in the scalp area?

CHAIRMAN JAMIESON.—Scratching will definitely spread the infection, so this must be prevented. It is advisable to clip the hair before applying an ammoniated mercury ointment.

DR. E. E. MARTMER, DETROIT.—Is an olive oil base for an ammoniated mercury ointment more effective because of its greater penetration?

CHAIRMAN JAMIESON.—This would be true in a ringworm infestation, but is not necessary in impetigo which is so superficial.

DR. H. F. MEYER, CHICAGO.—Is mercurial poisoning a factor to consider in extensive use of an ammoniated mercury ointment?

CHAIRMAN JAMIESON.—Very definitely. This is particularly true in infants where a general application of the ointment as a prophylactic measure might be employed.

DR. CRAIG.—Is ammoniated mercury effective in treating ringworm of the scalp?

CHAIRMAN JAMIESON.—This may be very satisfactory for some cases; at other times it does no good and it may be necessary to use 1 to 2 per cent iodine crystals in oil, which sometimes is very irritating.

DR. L. O. GODLEY, FORT WORTH.—I shave the affected area and use ultraviolet light.

CHAIRMAN JAMIESON.—My experience with ultraviolet light is that it is not as effective as x-ray therapy. You have to produce a certain amount of stimulation and irritation; get rid of the hairs and use a fungicide at the same time to get the best results.

DR. CRAIG.—What is a good fungicide?

CHAIRMAN JAMIESON.—Most of these are fungistatic instead of fungicidal. Get rid of the hair, and then use iodine or mercury or even Whitfield's ointment. In general, I prefer to use x-ray therapy for fungous infections, and ultraviolet therapy for pyogenic infections. Thallium acetate is used in widespread fungous infections of the scalp, but there have been very serious accidents. You must weigh the dosage accurately and weigh the child accurately and give 7 mg. per kilogram of body weight, or you won't have any patient to treat.

DR. J. W. BRITTON, ANNISTON, ALA.—What are the toxic symptoms from thallium acetate poisoning?

CHAIRMAN JAMIESON.—They are variable in severity from a toxemia to death.

DR. GIPSON.—What do you suggest for the relief of the itching in urticaria?

CHAIRMAN JAMIESON.—That is what the patient wants to know. Adrenalin is frequently used, but it has a short though rapid effect. Soda solutions or soda paste applied locally are often effective. Ephedrine either alone or combined with amytal is useful; a 0.5 per cent solution of carbolic acid applied locally may give relief. A saline cathartic is a usual method of treatment if there is any question of a food's being responsible for the urticaria, although there are many other possibilities as etiological factors in producing these lesions, such as heat, cold, etc.

DR. T. L. BIRNBERG, ST. PAUL.—I had one patient who almost died from the use of adrenalin in oil. After using it, I found that the child was allergic to peanuts and the preparation usually used is a peanut oil.

CHAIRMAN JAMIESON.—That is true. Once you inject something into the skin, it is rather difficult to take it out again.

DR. J. J. YORK, SCHENECTADY, N. Y.—What about the use of x-ray in the treatment of acne if other procedures fail?

CHAIRMAN JAMIESON.—Nothing is better if used properly and at the right time; from 80 to 90 per cent good results may be expected. There are many other factors to be considered, however, before resorting to this method of treatment; then it should be given in proper dosage over a period of from three to four months in weekly doses. I do not like to use this in young patients, but prefer to wait until they are 18 or 20 years old before resorting to this treatment.

DR. A. S. TRAISMAN, CHICAGO.—I would like to ask about diaper rash due to an ammoniacal urine.

CHAIRMAN JAMIESON.—This is the same problem as a contact dermatitis. Change diapers as soon as wet. The best application to use is some oil-soluble grease such as we use in occupational contact dermatitis; then put powder on that.

DR. C. L. LAMAR, BIRMINGHAM, ALA.—What about formaldehyde solutions for the feet?

CHAIRMAN JAMIESON.—The patient is very apt to develop contact dermatitis from its use, so try to keep away from formaldehyde, except formaldehyde gas for sterilizing the shoes.

DR. G. M. CLINE, BLOOMINGTON, ILL.—Do you believe that everyone can contract ringworm of the feet?

CHAIRMAN JAMIESON.—Without any question we have seen an increase in the amount of ringworm. We are finding in many of these cases organisms that are supposed to be nonpathogenic. This would indicate that many of these organisms have become capable of growing on human skin. Some may be on an allergic basis; on the other hand, some persons who have repeated exposures do not contract ringworm.

DR. R. A. KNOX, WASHINGTON, PA.—What prophylactic solution do you recommend in gymnasiums?

CHAIRMAN JAMIESON.—With hypochlorite solutions and the like, the contact is so brief that it does little if any good. These persons should dry their feet thoroughly and not go barefoot anywhere.

DR. ROGERS.—How about the efficacy of ivy extracts?

CHAIRMAN JAMIESON.—You must use them as you would for desensitization for hay fever or asthma, and repeat them every year. Some get excellent results with injections immediately after the start of the infection. It is harmless, although some districts have reported that the extracts cause an exacerbation of symptoms. Considerable diversity of opinion prevails at present regarding the value of pollen extracts in their use both as prophylactic and therapeutic measures.

Academy News

Region IV of the American Academy of Pediatrics will hold its next regional meeting on May 1, 2, and 3, 1941, at the Fairmont Hotel, San Francisco, Calif.

News and Notes

Dr. Katherine Bain, of St. Louis, has been appointed Director of the Division of Research in Child Development of the Children's Bureau of the United States. She succeeds Dr. Ethel Dunham, who has resigned to devote her time to writing. Dr. Bain was graduated from the University of Missouri in 1921 and received her M.D. degree from Washington University in 1925. She interned at the San Francisco and St. Louis Children's Hospitals. In recent years she has been Instructor in Clinical Pediatrics at the Washington University School of Medicine, St. Louis, and Physician-in-Chief to its Children's Allergy Clinic. She has contributed numerous papers to the literature of allergy in children.

A postgraduate course in pediatrics, under the direction of Professor Paul Letondal of the University of Montreal, was held at the Misericordia Hospital, 1051 St. Hubert St., Montreal, from Sept. 3 to 7, 1940.

Eighteen lectures on the subject "Nutritional Disorders in Infancy" were given, with the assistance of Professor Hector Sanche, Professor Gaston Gosselin, Dr. Daniel Longpré, Dr. Albert Guilbeault, Dr. Henri Charbonneau, Dr. Albert Jutras, Dr. Gilbert Brisebois, and Dr. Emile Hébert. Demonstration of patients and of the results achieved at the Misericordia Hospital followed. The course opened on Tuesday, Sept. 3, under the honorary presidency of the Honorable Henri Groulx, Minister of Health.

Dr. C. A. Aldrich has been appointed Chief of Staff of the Children's Memorial Hospital in Chicago, to succeed Dr. Joseph Brennemann who resigned some time ago. Dr. Aldrich's service will start January 1.

Book Review

Mineral Metabolism. Alfred T. Shohl, M.D. New York, 1939, American Chemical Society Monograph Series, Reinhold Publishing Corporation. Pp. 384. Price $5.

This book contains an immense amount of information relative to the role of the minerals in the structure and function of the human body. In addition to an author and subject index, there are thirteen chapters dealing with the following subjects: Mineral Composition of the Body; Secretions and Excretions; Internal Secretions; Total Base, Chloride, Ammonium and Bicarbonate; Calcium and Magnesium; Phosphorus; Sulfur; Iron; Iodine; Traces; Water Metabolism; Anion-Cation Relationships and Mineral Intakes; Balances and Requirements.

Because of its concise readable form, in attempting to simplify and clarify a field undergoing rapid expansion, and because of the factual information presented and the comprehensive bibliography, this book should appeal to all students, teachers, and research workers interested in mineral metabolism.